A STUDY ON PREVALENCE OF LEFT VENTRICULAR DYSFUNCTION AND ITS CORRELATION WITH ESTIMATED GLOMERULAR FILTRATION RATE (eGFR) IN CKD PATIENTS

DISSERTATION SUBMITTED FOR

DOCTOR OF MEDICINE

BRANCH - I (GENERAL MEDICINE)

APRIL 2015

THE TAMILNADU

DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"A STUDY ON PREVALENCE OF LEFT VENTRICULAR DYSFUNCTION AND ITS CORRELATION WITH ESTIMATED GLOMERULAR FILTRATION RATE (eGFR) IN CKD PATIENTS"** submitted by **DR. TINA ANN ANTONY** to the Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.D Degree Branch I (General Medicine) is a bonafide research work carried out by her under my direct supervision & guidance.

Captain Dr. B. Santhakumar
M.Sc (F.Sc), M.D(F.M), PGDMLE, Dip.N.B (F.M),
The Dean,
Madurai Medical College,
Government Rajaji Hospital,
Madurai

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"A STUDY ON PREVALENCE OF LEFT VENTRICULAR DYSFUNCTION AND ITS CORRELATION WITH ESTIMATED GLOMERULAR FILTRATION RATE (eGFR) IN CKD PATIENTS"** submitted by **DR. TINA ANN ANTONY** to the Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the requirement for the award of M.D Degree Branch I (General Medicine) is a bonafide research work carried out by her under my direct supervision & guidance.

Dr. S.Vadivel murugan M.D,
Professor and HOD,
Dept. of General Medicine,
Government Rajaji Hospital,
Madurai Medical College,
Madurai.

Dr.V.T. PREMKUMAR M.D.,
Professor of Medicine
Dept. of General Medicine,
Government Rajaji Hospital,
Madurai Medical College,
Madurai.

DECLARATION

I, **Dr. TINA ANN ANTONY** declare that, I carried out this work on, **"A STUDY ON PREVALENCE OF LEFT VENTRICULAR DYSFUNCTION AND ITS CORRELATION WITH ESTIMATED GLOMERULAR FILTRATION RATE (eGFR) IN CKD PATIENTS"** at the Department of Medicine, Govt. Rajaji Hospital during the period of July 2013 to August 2014. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, diploma to any other University, Board either in India or abroad.

This is submitted to The Tamilnadu Dr.M.G.R.Medical University, Chennai in partial fulfilment of the rules and regulations for the M.D degree examination in General Medicine.

Place : Madurai **Dr. TINA ANN ANTONY**

Date :

ACKNOWLEDGEMENTS

At the outset, I wish to thank our Dean, **Captain Dr. B. Santhakumar, M.Sc (F.Sc), M.D(F.M), PGDMLE, Dip.N.B (F.M),** for permitting me to use the facilities of Madurai Medical College and Government Rajaji Hospital to conduct this study.

My beloved Head of the Department of Medicine, **Prof. *Dr.S.Vadivel Murugan M.D***., has always guided me with his valuable words of advice and has encouraged innovative thinking and original research work done by post graduates.

I shall remain eternally grateful to my unit chief ***Prof. Dr. V.T.Premkumar M.D,*** who has given me his moral support and encouragement through the conduct of the study.

I also sincerely thank our beloved professors ***Dr.R.Balajinathan M.D, Dr.M.Natarajan M.D, Dr.Bagialakshmi M.D, Dr.J.Sangumani. M.D, Dr.C.Dharmaraj M.D.,*** and ***Dr.R.Prabhakaran M.D,*** for their par excellence clinical teaching and constant support.

I am extremely grateful to the Department of Nephrology and ***Prof. Dr.Shanmuga Perumal M.D D.M*** for their constant support, guidance, cooperation and encouragement.

I would also like to express my deep felt gratitude to Department of Cardiology and ***Dr.A.S.Arul M.D D.M*** and retired professor and H.O.D of Cardiology ***Dr.R.A. Janarthanan M.D D.M*** for their support, encouragement and guidance.

I offer my heartfelt thanks to my unit ***Assistant Professors Dr.K.S. Maniappan M.D., Dr. M.Sooryakumar, M.D, and Dr. P.Manimegalai M.D,*** for their constant encouragement, timely help and critical suggestions throughout the study.

I would also like to sincerely thank the ***Department of Biochemistry*** for helping me out with the laboratory investigations.

My patients, who form the most integral part of the work, were always kind and cooperative. I pray to God to give them courage and strength to endure their illness.

I thank my friends and family who have stood by me during my times of need. Their help and support have always been invaluable to me. And last but not the least I would like thank the Lord Almighty for His grace and blessings without which nothing would have been possible.

ABBREVIATIONS

CKD	Chronic Kidney Disease
GFR	Glomerular Filtration Rate
LV	Left Ventricular
LVH	Left Ventricular Hypertrophy
CAD	Coronary Artery Disease
eGFR	estimated Glomerular Filtration Rate
NKF	National Kidney Foundation
KDOQI	Kidney Disease Outcome Quality Initiative
SEEK	Screening and Early Evaluation of Kidney disease
TGF β	Transforming Growth Factor β
FGF - 23	Fibroblast Growth Factor - 23
PTH	Parathormone
CRP	C Reactive Protein
ECF	Extracellular Fluid
ACE	Angiotensin Converting Enzyme
ARB	Angiotensin Receptor Blocker
HIV	Human Immunodeficiency Virus
RAAS	Renin Angiotensin Aldosterone System

NHANES	National Health and Nutrition Evaluation Survey
MRFIT	Multiple Risk Factor Intervention Trial
ADMA	Asymmetric Dimethyl Arginine
ECHO	Echocardiography
BP	Blood Pressure
MDRD	Modified Diet in Renal Disease
BMI	Body Mass Index
PICP	Peptide of collagen type 1 Protein
CT -1	Cardiotrophin -1
DD	Diastolic dysfunction
SD	Systolic dysfunction

CONTENTS

TOPIC	PAGE NO.
1. INTRODUCTION	1
2. AIMS AND OBJECTIVES	6
3. REVIEW OF LITERATURE	7
4. METHODS AND MATERIALS	73
5. OBSERVATION AND RESULTS	78
6. DISCUSSION	92
7. SUMMARY	98
8. CONCLUSION	100
9. ANNEXURE • *Bibliography* • *Proforma* • *Master chart* • *Ethical clearance* • *Turnitin Certificate*	

ABSTRACT

BACKGROUND AND OBJECTIVE:

In Chronic Kidney Disease there is a higher incidence cardiovascular events. Most of the patients with CKD succumb to cardiovascular disease even before they reach the end stage of renal disease. Hence all efforts should be given in earlier stages of CKD to prevent the development of cardiovascular complications.

LV diastolic dysfunction is found to antedate LVH and systolic dysfunction. It is not just associated with hemodynamic factors like anaemia and hypertension, but also with uraemia related non hemodynamic factors like secondary hyperparathyroidism, altered mineral metabolism, cardiotrophysin etc.

ECHO provides a simple non-invasive method to assess the left ventricular structure and function, which helps us in identifying those prone for cardiovascular complications at an earlier stage of CKD.

This study was done to find out the prevalence of LV dysfunction and its correlation with eGFR in CKD patients.

METHODS:

50 hypertensive CKD patients and 50 normotensive CKD patients admitted to Government Rajaji Hospital between May 2013 to August 2014 were evaluated

for the presence of LV dysfunction and LVH and the results were compared with that of 50 age and sex matched individuals.

Patients with acute kidney injury, prior coronary artery disease, valvular heart disease, cardiomyopathy, diabetic individuals and CKD patients on renal replacement therapy or transplant patients were excluded from the study.

The CKD patients were divided into various stages of CKD based on their eGFR (calculated according to MDRD formula) and they were evaluated by ECHO. Those with an ejection fraction < 50% were considered to have systolic dysfuction. Diastolic dysfunction was calculated based on the E/A ratio. E/A ratio <0.8 was grade I, 0.8 – 1.5 was grade II and >2 was grade III diastolic dysfunction. This was compared with the ECHO findings of the controls. The collected data was analysed using various statistical methods.

RESULTS:

74% of CKD patients had LV diastolic dysfunction ($p < 0.0001$). Diastolic dysfunction was found to occur in 84% of the hypertensive CKD and in 64% of the normotensive CKD ($p=0.02$).

Comparing the CKD normotensives with the control group, 64% among the normotensive CKD had diastolic dysfunction whereas only16% of controls had diastolic dysfunction ($p<0.05$).

There is a negative correlation between the eGFR and diastolic dysfunction.So as the eGFR falls, the diastolic dysfunction increases.

INTERPRETATION AND CONCLUSION:

Even in the absence of hypertension, LV diastolic dysfunction can occur in CKD. This emphasizes the need for correction of not just hemodynamic factors but also the uraemia related factors.

KEY WORDS:

Chronic Kidney Disease, Left ventricular diastolic dysfunction, ECHO, eGFR

INTRODUCTION

Chronic kidney disease (CKD) is a spectrum of pathophysiological process that is associated with dysfunction of kidney and a progressive decrease in Glomerular Filtration Rate (GFR). [1]

It refers to functional or structural abnormalities of kidneys for more than three months, irrespective of cause.

It is a global health concern. CKD has been the 12th leading cause of death, and the 17th leading cause of disability. CKD has a number of co-morbidities and hence is a disease with high mortality.[2]

An analysis of risk factors for development and progression of CKD is necessary in clinical practice.

The result of CKD is loss of kidney function which in the long run leads to kidney failure, decreased kidney function and its complications, development of cardiovascular disease and death.[3] Improving outcomes in CKD requires prevention, detection, evaluation, and management of other chronic diseases, such as hypertension, hypercholesterolemia , diabetes and obesity.

The number of CKD patients is on the rise. The prevalence rate of CKD in India is not available due to lack of adequate data recording. In community based studies, the prevalence rate of CKD is from 0.79% to 1.4%. The studies were done to detect stage 3 CKD or worse. The exact prevalence is higher than the one reported. The end stage renal disease (ESRD) incidence is reported as 160 to 232 per million population and the projected ESRD prevalence rate was 785 to 870 per million population.[4]

Screening and Early Evaluation of Kidney disease (SEEK); a community based study which was done recently reported a very high prevalence rate of CKD which is about 17.4%.[5] The Indian CKD registry was formed in the year 2005 with a target to serve as a comprehensive nationwide data warehouse for studying the different aspects of CKD. The data house has enrolled about 63,538 patients and 74% of the cases have CKD stage 4 and stage 5.

The prevalence of End Stage Renal Disease [4] (ESRD) and the patients who are on renal replacement therapy has increased since last 2 decades. Only 20% of ESRD patients are on Renal Replacement Therapy (RRT). It is estimated that 1,00,000 new patients of ESRD undergo renal replacement programs every year in India.

The most common cause for CKD in India is Diabetes. It accounts for about 30 to 40% of patients. With the increasing number of diabetic patients there is a parallel increase in the incidence of CKD. In India the number of patients with diabetes is now about 41 million and is on the rise. Most of the patients develop diabetic nephropathy and land up in ESRD.

In Chronic Kidney Disease there is a higher incidence of cardiovascular events. Cardiovascular disease is one of the prime causes of morbidity and mortality in all the stage of CKD. Most of the patients with CKD develop cardiovascular disease before reaching ESRD. The CKD registry [6] has shown that patients with CKD stage 4 have a high incidence of cardiovascular complications. Most of the patients die before they have ESRD. Patients in early stages of CKD are also found to have a high cardiovascular morbidity. Hence we should look into the prevention of cardiovascular complications.

A large cohort study of patients with CKD stages 2 to 4 showed that death was seen more often than progression to kidney failure in all stages of CKD. There was a high baseline prevalence of cardiovascular disease in the patients who died, compared to those who survived, which suggests that cardiovascular disease accounted for a huge proportion of

the deaths. Hence, most patients in the earlier stages of CKD do not progress to kidney failure because of the mortality caused due to cardiovascular disease. Cardiovascular disease has been seen as a major "competing outcome or risk" of kidney failure. [3]

The cardiovascular manifestation in CKD includes: [13]

- Ischemic heart disease – myocardial infarction and angina
- Left ventricular hypertrophy
- Heart failure : LV diastolic and systolic dysfunction and
- Dilated cardiomyopathy.

Heart and kidney are linked to each other in the hemodynamic and regulatory functions. There are multiple communications among the two organs like Sympathetic Nervous System, Anti Diuretic Hormone, Renin Angiotensin Aldosterone System and natriuretic peptides.[8] National Kidney Foundation formed a Task Force which considered Coronary Artery Disease (CAD) and LVH as the target conditions, recommended for decreasing cardiovascular mortality in ESRD.[9]

LVH is associated with both systolic and diastolic dysfunction. LVH associated with systolic dysfunction is expressed by decreased mid wall systolic fractional shortening and decreased ejection

fraction. These findings show us that mild reduction in the renal perfusion which is caused by the slightly impaired LV systolic function, is associated with pathological, highly pulsatile perfusion in the microvasculature of the kidney. This might be the mechanism through which a progressive reduction of renal function takes place in patients with pre-existing renal damage. This renal insufficiency produced, adversely affects the function of the heart, which produces a vicious cycle where the renal failure further impairs cardiac performance.

Diastolic dysfunction is associated with higher incidence of episodes of intradialytic hypotension and higher peri-operative death from pulmonary oedema at the time of renal transplantation. It is significant to recognize and correct the cardiovascular complications and risk factors before the commencement of dialysis.

Echocardiography will provide us with a very simple and non-invasive assessment of the structure and function of the heart. It also helps us to identify the people who are at greater risk. Strategies to prevent the development and progression of LV dysfunction at an early stage may prove more effective.

AIMS AND OBJECTIVES:

1. To assess the prevalence of Left Ventricular (systolic and/ or diastolic) dysfunction in patients with CKD.
2. To evaluate the correlation between Left Ventricular dysfunction and eGFR in CKD patients
3. To compare the Left Ventricular dysfunction in hypertensive and normotensive CKD patients.

REVIEW OF LITERATURE

NORMAL ANATOMY AND PHYSIOLOGY OF KIDNEY

EMBRYOLOGY OF KIDNEY:

The kidney is one of the most highly differentiated organs in the body [10] They develop from the intermediate mesoderm under the timed and sequential control of genes. The excretory tubules (nephrons) develop from the metanephric blastema. The collecting part arises from the ureteric bud, which arises from the lower part of mesonephric duct. The ureteric bud grows cranially towards the metanephric blastema, and becomes dilated to form an ampulla. Ampulla undergoes division to form the major calyces, then minor calyces and finally the collecting tubules. [11]

GROSS ANATOMY:

Kidneys are a pair of excretory retroperitoneal organs, situated on each side of the vertebral column. It consists of two poles, extending from T12 to L3. The left kidney is at a lower level than the right. The approximate size of each kidney is 11 cm long, 5 cm wide and 3 cm in thickness. The weight of a single kidney is about 125 to 170 grams. Each kidney is surrounded by a fibrous capsule with perirenal pad of fat.

Renal vessels, renal pelvis, lymphatics and nerve plexus enter through the hilum. Kidney consists of an outer cortex and an inner medulla. Cortex contains all the glomeruli and portions of the tubules, whereas the medulla is made of renal pyramids and renal columns. Minor calyx arises from the pyramids and joins to form the major calyces which form the renal pelvis. [10]

THE NEPHRON:

Nephrons are the functional units of kidney. Kidney contains approximately about 1.2 million nephrons. The nephron consists of malphigian or renal corpuscle (Bowman's capsule and the glomerulus), the site at which blood is filtered and a renal tubule (the proximal tubule, thin and thick ascending limb, distal tubule and collecting ducts) from which solutes are reabsorbed. [10]

Glomerulus (Renal corpuscle):

- It is a network of capillaries lined by endothelial cells, central mesangial cells, visceral epithelial cells and its basement membrane, parietal layer of Bowman's capsule with its basement membrane.

- Visceral epithelium becomes continuous with the parietal epithelium at the vascular pole. Here the afferent arteriole enters and efferent arteriole exits. [10]

- It also helps in the production of an ultrafiltrate of plasma

Tubules:

- Continues from Bowman space and consists of proximal loop of Henle and distal tubule.

- The proximal convoluted tubule is lined by cuboidal cells which aids in the absorption of solutes.

- Loop of Henle is made of a thin descending limb and a thick ascending limb, extending into cortex. The thick end of ascending limb reaches the glomerulus of the nephron and nestles between its afferent and efferent arterioles. Specialised cells at the end form the macula densa, particularly close to the afferent arteriole.[12]

- The macula densa, the neighboring lacis cells, and the renin-secreting juxtaglomerular cells which are present in the afferent arteriole form the juxtaglomerular apparatus [12]

- Distal convoluted tubules coalesce to form the collecting ducts. The epithelium of collecting duct has principal (P cells) and intercalated (I cells). P cells are involved in Na+ reabsorption and vasopressin stimulated water reabsorption. The I cells are concerned with acid secretion and HCO3- secretion.[12]

VASCULAR SUPPLY OF KIDNEY:

Kidney is supplied by a single renal artery, a direct branch from abdominal aorta. Renal artery enters the hilum and divides into an anterior and a posterior branch.

- Lobar arteries: these are 3 segmental arteries arising from the anterior branch and supply upper, middle and lower third of the anterior surface of the kidney. Posterior branch supplies posterior half. These are end arteries and no collateral circulation has been demonstrated.[10]

- Inter lobar arteries: arises from the lobar arteries runs between the renal columns and pyramids.

- Arcuate arteries: arises from the interlobar arteries.

- Interlobular arteries: arises from the arcuate arteries and forms the afferent arterioles.

FUNCTIONS OF THE KIDNEY: [11]

A. Maintain solute and water homeostasis.

B. Serves as an endocrine organ by producing erythropoietin, active form of vitamin D and renin.

C. Excretion of metabolic products.

D. Regulation of blood pressure and intraglomerular hemodynamics.

E. Regulation of acid bases.

F. Elimination of toxic substances from the body.

G. Involved in catabolism of small peptide hormones.

H. Regulation of extra cellular volume and osmolarity.

AGE RELATED CHANGES OF KIDNEY:

The kidney attains its full anatomical and functional maturity by the end of 3rddecade of life. From then on, involutive changes start. Up to 6th decade these changes are slow and after this a rapid progression occurs due to reduced renal perfusion. Despite this, under normal circumstances these changes do not show any signs of renal insufficiency. [10]

KIDNEY IN YOUNG ADULTS:

Anatomical characteristics:

During this period, there is full maturation of all renal structures. The cortico-medullary index (cortex: medulla) increases from 1.64:1 in the new born to 2.59:1 in adults. The kidneys reach their maximum size during this period. [10]

Functional characteristics:

The kidneys are fully functional in adults due to its complete maturation. The normal Glomerular Filtration Rate (GFR) at this period is 120 to 130 ml/min/1.73m^2. GFR decreases as age advances.[10]

KIDNEY IN THE ELDERLY:

Anatomical characteristics:

Age produces changes that are similar to those in chronic kidney diseases. There is a progressive loss of kidney mass. The weight of both the kidneys decreases to 110 – 120 gram as the age increases. The lost kidney mass is mainly in the cortex, characterised by a reduction in the number of functional nephrons, whereas medulla is relatively spared. There is an enlargement of the mesangial matrix, thickening of the basement membrane and hyalinised arterioles, with a gradual reduction in

the renal corpuscles. With ageing, renal vasculature undergoes changes regardless of hypertension or other diseases. The renal arteries undergo sclerosis resulting in ischemic nephropathy.

Functional characteristics:

In normal healthy persons the age related changes develop slowly. Increase in vascular resistance in the afferent and efferent arterioles decreases renal blood flow. There is a progressive decrease in the intensity of glomerular filtration. The creatinine clearance decreases at an average of 0.83ml/min/m^2 per year. However serum creatinine does not change as there is a progressive decline in the muscle mass. The sodium preserving capacity is lowered due to its insufficient intake and there is reduced reabsorption of sodium by the distal tubules due to interstitial fibrosis. The renin-angiotensin-aldosterone system activity is reduced. The concentrating and diluting capacity of kidney is also reduced.

ADAPTATION OF KIDNEYS TO NEPHRON LOSS

The kidney's ability of maintaining constancy of the extracellular fluid volume and composition is usually well preserved till late in the course of CKD. When nephrons are lost through disease, the rest of the nephrons undergo physiological changes resulting in hypertrophy and

hyperfunction, which compensates for the loss. Studies in patients with CKD showed that; if the GFR falls below a critical level, the disease leads to end stage; even when initial disease activity has been controlled. This mechanism for the disease progression of CKD has been based on the Bricker's intact nephron hypothesis, which states that:

"As CKD progresses; the kidney function is maintained by a decreasing pool of hyperfunctioning nephrons rather than a relatively constant number of nephrons with decreasing function".

RENAL PROGRESSION: [13]

Renal progression is a term used to define primary nephron loss which produces a maladaptive deterioration in the remaining nephrons. Irrespective of injury in the glomeruli or tubulointerstitium, it follows a common pathway. The mechanisms involved are:

- Glomerular hypertension reduces the single nephron GFR and the associated proteinuria.
- Proteinuria produces accumulation of interstitial mononuclear cells.
- Activation of nephritogenic T lymphocytes produces interstitial nephritis.

- Epithelial – mesenchymal transition forming new interstitial fibroblasts.
- Fibrosis of adjacent capillaries and tubular nephrons results in acellular scar.

ROLE OF ANGIOTENSIN II IN RENAL PROGRESSION:

Angiotensin hastens renal progression in CKD patients. Aldosterone increases the renal vascular resistance and glomerular capillary pressure which complements the detrimental effects of Angiotensin. It causes renal damage by:

- Efferent arteriolar vasoconstriction which increases the intraglomerular capillary pressure.
- By selectively altering the glomerular size it induces protein ultrafiltration.
- Podocyte function is altered by increasing intracellular calcium.
- Oxidative stress in the surrounding renal tissues.

TUBULAR FUNCTION IN CHRONIC RENAL FAILURE:

The loss of functioning nephrons in chronic renal failure produces a persistent intraglomerular hypertension.

Glomerulotubular balance is maintained; inspite of loss of functioning nephrons, by which the remaining nephrons increases the single nephron glomerular filtration. To maintain the solute homeostasis the tubular function is altered in CKD. [14]

1. SODIUM:

The transport of sodium and its ability to maintain extracellular volume is well preserved till late in CKD. Sodium excretion is increased by decreasing its reabsorption in the Henle's loop and distal nephrons. There is increased excretion of organic and inorganic anions, and increased expression of atrial natriuretic peptide . As the disease progresses, compensatory changes are lost resulting in sodium retention, expansion of intravascular volume, oedema and worsening hypertension. [14]

2. Potassium:

Hyperkalemia can occur when the compensatory functions of the tubules are lost.

1. Urinary dilution and concentration:

CKD patients lose their ability to concentrate or dilute the urine. So the urine specific gravity is fixed and the patients are prone for nocturia.

2. Acid base regulation:

The solute load of the remaining nephrons is increased which produces impaired total body H+ excretion. The hydrogen ion pumps are lost with reduction in ammoniagenesis resulting in non-delta acidosis. In advanced stages, the ammoniagenesis is further decreased by elevated potassium resulting in type IV renal tubular acidosis.

3. Calcium and phosphate:

Kidneys and intestines are the key regulators of calcium phosphate metabolism. In chronic renal failure the excretion of phosphate is reduced resulting in hyperphosphatemia. Calcium level is reduced by the following ways:

1. Decreased absorption in the gut

2. Decreased calcitriol formation

3. Increased serum phosphate

4. Increased parathyroid hormone release.

CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) includes a spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR).[2]

Chronic Renal Failure is a term used for the continuing significant irreversible reduction in nephron number and corresponds to CKD stages 3 – 5. [12]

End-Stage Renal Disease (ESRD) is defined as a stage of CKD where toxins, electrolytes and fluids which are normally excreted by kidney are accumulated and it is responsible for uremic syndrome. Which ultimately leads to death of the patient unless a renal replacement therapy using dialysis or renal transplantation is done where, the toxins are removed. [12]

The kidney functions as biosynthetic, excretory and metabolic organs, necessary for maintaining normal physiology. Although daily dialysis can replace some kidney functions, it cannot replicate the normal biosynthetic and metabolic activities of the kidney. [12]

DEFINITION OF CHRONIC KIDNEY DISEASE:

The National Kidney Foundation's (NKF) "Kidney Disease Outcomes Quality Initiative (KDOQI)" has proposed a definition and classification scheme of CKD. The NKF guidelines define CKD on the basis of kidney damage and or reduced renal function. [2]

Glomerular filtration rate is calculated from serum creatinine and equations with the help of age, sex, race, and BMI. CKD can be classified based on the level of GFR . [1] Stages 1 and 2 are kidney damage, stages 3 and 4 are decreased kidney function and stage 5 is kidney failure. [3]

CRITERIA: [2, 1, 13]

1. Kidney damage ≥ 3 months, either functional or structural abnormalities, with or without decreased GFR, are seen by the following manifested

    - Pathological abnormalities or
    - Markers of kidney damage

        i. Urinary abnormalities (proteinuria).

ii. Imaging abnormalities. (Bilaterally shrunken kidneys)

iii. Blood abnormalities.

2. GFR <60 ml/min/1.73m^2 for 3 months or longer and with or without kidney damage.

CLASSIFICATION OF CKD:

STAGE	GFR / ml / 1.73 m2	ACTION
0	>90 a	Screening: CKD risk reduction
1	>90 b	Diagnosis and treatment • Slowing the progression of the disease • Treatment of comorbidities • CVD risk reduction
2	60 -89	Estimating progression
3	30 – 59	Treating complications
4	15 – 29	Prepare for kidney replacement
5	<15	Kidney replacement

a - risk factors for CKD

b - demonstrated kidney damage – persistent proteinuria,

abnormal urine sediment,

abnormal blood and urine chemistry,

abnormal imaging studies [13]

Staging of CKD was based on the estimated glomerular filtration rate (eGFR) and not on serum creatinine level. In stage 1 and stage 2 the GFR is normal or near normal, so the patient must have an accompanying

structural or functional defect (eg, proteinuria, or abnormal imaging studies) to classify under it.

RISK FACTORS FOR CKD: [14]

Hypertension

Diabetes mellitus

Autoimmune disease

Older age

African ancestry – genetic – APOL 1 gene

Family history of renal disease

Previous episode of acute kidney injury

Proteinuria

Abnormal urine sediment

Structural abnormalities of the urinary tract

Nephrotoxins

Dyslipidemia

Smoking

PATHOPHYSIOLOGY OF CHRONIC KIDNEY DISEASE:

It's divided into two causes

1) **Initiating mechanism**

2) **Progressive mechanisms**

- Initiating mechanisms – this is caused due to a specific etiology. For example genetically determined abnormalities in the renal integrity or its development, immune complex deposition and inflammation in certain types of glomerulonephritis, toxin exposure in interstitial nephritis etc

- Progressive mechanisms –this is caused due to the hyperfiltration and hypertrophy of the remaining viable nephrons due to decreased renal mass, irrespective of etiology. These responses were mediated by the cytokines and growth factors, vasoactive hormones, and transforming growth factor (TGFß). [13]

The increased intra-renal renin activity contributes to both initial inciting event and also to the progressive mechanisms, finally leading on to the glomerular sclerosis and renal failure.

Risk Factors for Chronic kidney disease and its outcome [14]

Risk Factors	Definition	Examples
Susceptibility factors	Increase susceptibility to kidney damage	Older age Family history of Chronic reduction in kidney mass low birth weight kidney disease
Initiation factors	Directly initiate kidney damage	Diabetes high blood pressure autoimmune diseases urinary stones lower urinary tract obstruction, systemic infections urinary tract infections drug toxicity
Progression factors	Cause worsening kidney damage and faster decline in kidney function after initiation of kidney damage	poor glycemic control in diabetes Higher level of proteinuria smoking systolic blood pressure
End-stage factors	Increase morbidity and mortality in kidney failure	Lower dialysis dose low serum albumin level (Kt/V) temporary vascular access anemia

Examples of Epidemiologic Studies Involving Patients with Kidney Disease

Study Design	Examples
Prospective cohorts	Population Based Cohorts Atherosclerosis Risk in Communities Study (ARIC) Framingham Heart Study Cardiovascular Health Study (CHS) Multi-Ethnic Study of Atherosclerosis (MESA) Health, Aging and Body Composition (Health ABC) Coronary Artery Risk Development in Young Adults (CARDIA) Cohorts of Patients with Kidney Disease Chronic Renal Insufficiency Cohort (CRIC) Cardiovascular Risk in Birmingham (CRIB) United States Renal Data System (USRDS) Choices for Healthy Outcomes in Caring for End Stage Renal Disease (CHOICE)
Intervention trials	Trials in Patients with Kidney Disease Modification of Diet in Renal Disease Study (MDRD) African American Study of Kidney Disease (AASK) Study of Heart and Renal Protection (SHARP) Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) The Microalbuminuria Captopril Study GruppoItaliano di StudiEpidemiologici in Nefrologia (GISEN)

Study Design	Examples
	Deutsche Diabetes DialyseStudie (4D) Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Irbesartan in Diabetic Nephropathy Trial (IDNT) Hemodialysis Study (HEMO) The Ramipril Efficacy In Nephropathy (REIN) Post Hoc Analysis of Trials in Populations with CVD or CVD Risk Factors Heart Outcomes Prevention Evaluation Trial (HOPE) Cholesterol and Recurrent Events Trial (CARE) Antihypertensive and Lipid-Lowering Treatment t Prevent Heart Attack Trial (ALLHAT)

CAUSES OF CHRONIC KIDNEY DISEASE:

Diabetic glomerulosclerosis	
Hypertensive nephrosclerosis	
Glomerular Diseases	Systemic lupus erythematosus.
	Amyloidosis, light chain disease.
	Glomerulonephritis
	Wegener's granulomatosis
Tubulointerstitial Diseases	Obstructive nephropathy (stones, benign prostatic hypertrophy).
	Analgesic nephropathy.
	Myeloma kidney.
	Reflux nephropathy.
Vascular Diseases	Atheroembolic renal disease
	Vasculitis.
	Scleroderma.
	Reno vascular renal failure
Cystic Diseases	Medullary cystic kidney disease
	ADPKD.

CLINICAL PRESENATION:

Usually the patients are asymptomatic in the early stages of CKD. Hypertension and proteinuria are the most common features of CKD and are present in all stages of the disease. Uraemia leads to disruption in the function of all organ systems. Most common complications include anaemia, decreased appetite, and abnormalities in potassium, sodium, water and acid-base homeostasis, abnormalities in phosphorus, calcium and mineral regulating hormone.[13]

PATHOPHYSIOLOGY AND BIOCHEMISTRY OF UREMIA:

1. Consequent to accumulation of toxins that are normally excreted:

Even though urea and creatinine measures the excretory capacity of kidney, it is not the accumulation of these toxins that are responsible for the uremic symptoms. The toxins that are implicated in uremic syndrome include: hydrophobic, protein bound, water soluble, charged and uncharged molecules. Additional nitrogenous excretory products include urates, hippurates, guanidino compounds, polyamines, products of nucleic acid metabolism, myoinositol, benzoates, indoles and phenols. Compounds called middle molecules (molecular mass of 500 – 1500 Da) also contribute to morbidity and mortality. [13]

2. **Consequent to loss of other renal functions:**

Suppression of metabolic and endocrine functions results in anemia, malnutrition, abnormal metabolism of protein, carbohydrates and fats. FGF 23, PTH, insulin, glucagon, Vitamin D, sex hormones all change with renal failure. It occurs due to abnormal retention, decreased degradation or abnormal regulation. [13]

3. **Progressive systemic inflammation and its vascular and nutritional consequences:**

   - Elevated CRP and acute phase reactants
   - Negative acute phase reactants- albumin and fetuin decline.

   So, the inflammation associated with CKD is important in malnutrition inflammation-atherosclerosis/calcification syndrome.

The clinical presentation depends on the organ system involved, the manifestations include:

1. Fluid, electrolyte and acid-base disorders:

Sodium and water homeostasis:

In the early stages of CKD, the total body content of sodium and water is increased. Dietary intake of sodium exceeds the urinary excretion resulting in sodium retention and extra cellular (ECF) volume expansion. Thus resulting in hypertension. Hyponatremia is not commonly seen in CKD patients, if it is present, it will respond to water restriction. Some patients may have impaired renal conservation of sodium and water. [13]

Potassium homeostasis:

Hyperkalemia in CKD may be due to the following mechanisms:

A. Increased dietary potassium intake.

B. Protein catabolism.

C. Haemolysis, haemorrhage

D. Transfusion of stored blood and

E. Metabolic acidosis.

F. Drugs – ACE inhibitors, ARBs, spironolactone, potassium sparing diuretics (amiloride, triamterene, eplerenone).

Hyporeninemic hypoaldosteronism, obstructive uropathy and sickle cell nephropathy may cause disruption of potassium secretory mechanism out of proportion to decline in GFR.

Hypokalemia is not common in CKD. It may occur in reduced dietary intake, excessive diuretic therapy, gastrointestinal losses, primary potassium wasting conditions – Fanconis syndrome, Renal Tubular Acidosis

Metabolic acidosis:

Commonly seen in patients with advanced CKD. The combination of hyperkalemia and hyperchloremic metabolic acidosis is often present. Non anion gap acidosis occurs in the early stages of CKD but in later stages as the disease progresses anion gap acidosis ensues. Treatment of hyperkalemia increases the renal ammonia production; improve the renal production of bicarbonate thereby improving the metabolic acidosis. [13]

Disorders of calcium and phosphate metabolism:

2. Bone manifestations of CKD:

Due to high bone turn over - secondary hyperparathyroidism produces Osteitis fibrosa cystica and low bone turn over produces

adyanamic bone disease and osteomalacia. Reduced GFR (< 60 ml/min) leads to reduced excretion of phosphate - retained phosphate stimulates PTH- secondary hyperparathyroidism. PTH is by itself a uremic toxin.[13]

Fibroblast growth factor 23(FGF-23) is a phosphatonin that promotes the renal phosphate excretion. Studies have shown that high levels of FGF-23 are an independent risk factor for left ventricular hypertrophy. Adynamic bone disease is most common in diabetics and elderly patients. It is also associated with cardiac and vascular calcification. Osteomalacia is caused by vitamin D deficiency, metabolic acidosis. Renal osteodystrophy results from secondary hyperparathyroidism. [13]

Hyperphosphatemia and hypercalcemia causes increased vascular calcification of the media of coronary arteries and heart valves and increased cardiovascular mortality. [13]

Calciphylaxis (calcific uremic arteriolopathy) due to vascular and soft tissue calcification can occur in advanced CKD.

3 Neuromuscular abnormalities:

It results in peripheral neuropathy, autonomic neuropathy and myopathy. These abnormalities are due to the nitrogenous metabolites and middle molecules. In the early stages patients present with disturbances in the memory, concentration and sleep. Neuromuscular irritability, including hiccups, cramps, and fasciculations or twitching of muscles are seen in later stages. Asterixis, myoclonus, seizures and coma may occur in advanced untreated cases. [13]

Peripheral neuropathy occurs from stage 4 of CKD and its evidence without any other cause is a firm indication for renal replacement therapy. Sensory nerves, lower extremities, distal parts are more involved than the motor, upper extremities and proximal part. 'Restless leg syndrome' is a common manifestation.

4. Gastrointestinal and nutritional manifestations:

Uremic fetor can lead to dysgeusia. Other manifestations include gastritis, peptic ulcer disease, and mucosal ulcerations resulting in abdominal pain, nausea, vomiting and GI bleeding. Constipation is common in CKD and is worsened by calcium and iron supplements.

Protein energy malnutrition due to low protein and calorie intake is common in advanced stages. Metabolic acidosis and activation of inflammatory cytokines promotes protein catabolism. All the patients should be assessed for malnutrition from stage 3 of CKD. [13]

5. Endocrine – metabolic manifestations:

Glucose metabolism is often impaired in CKD. Plasma insulin levels are elevated in most of the uremic patients as the kidneys fail to remove it. Due to the diminished degradation of insulin, insulin and hypoglycaemic agents require dose reduction.

In women with CKD, oestrogen levels are low. Menstrual abnormalities and infertility are common. Pregnancy may hasten the progression of the disease. Spontaneous abortions and miscarriages are common. Males have reduced plasma testosterone levels, sexual dysfunction and oligospermia. [13]

6. Dermatologic manifestations:

Pruritus is the most common and devastating complication of CKD. Hyper pigmentation of the skin due to the deposition of pigmented metabolites (urochromes) can occur. Nephrogenic fibrosing dermopathy occurs in patients exposed to gadolinium contrast. The

condition is characterised by progressive subcutaneous induration of arms and legs. [13]

7. Hematologic abnormalities:

Abnormal haemostasis:

Prolonged bleeding time

Decreased activity of platelet factor 3

Impaired prothrombin consumption

Abnormal platelet adhesion and aggregation

Thrombophilia occurs due to nephrotic range proteinuria, which results in hypoalbuminemia and renal loss of anticoagulant factors. [13]

ANAEMIA AND CHRONIC KIDNEY DISEASE

Anaemia is most common in CKD patients and the cause for anaemia is multifactorial. Even though considered as normocytic normochromic due to erythropoietin deficiency, other factors like iron deficiency contributes a major proportion and this is worsened in patients on dialysis.

Anaemia develops earlier in CKD patients with diabetes and it is more severe than with non-diabetic patients. The degree of anaemia reflects the severity of disease.

Based on KDOQI guidelines, anaemia in CKD is defined as haemoglobin less than 12 gm/dl for men & postmenopausal women and 11 gm/dl in premenopausal women.

In general anaemia becomes more frequent as renal function declines, becoming almost universal in ESRD. Studies have demonstrated correlation of anaemia with progression of renal failure. A randomized cohort study RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) reports that for every 1g/dl decrease in haemoglobin, the risk of developing renal failure increases by 11%.

ETIOLOGY OF ANAEMIA IN CKD:

1) Relative erythropoietin deficiency.
2) Iron deficiency (absolute/functional).
3) Decreased RBC survival.
4) Reduced dietary intake and absorption.
5) Bleeding diathesis.
6) Urinary loss of transferrin as a part of proteinuria leading to impaired iron transport.

CONTRIBUTORY FACTORS:

- Uremic toxins.
- Immunosuppressive drugs.
- Aluminium toxicity.
- Secondary hyperparathyroidism and bone marrow fibrosis.
- Folate and vitamin B12 deficiency.
- Associated HIV/HCV infections.
- Chronic inflammation and release of inflammatory cytokines.
- Haemoglobinopathy.
- Co-morbid conditions like hypo/hyperthyroidism, pregnancy, auto-immune diseases, HIV diseases.

MANIFESTATIONS OF ANEMIA:

- Decreased quality of life, fatigue and diminished exercise tolerance
- Decreased mental acuity and cognitive functions.
- Decreased tissue oxygen delivery and utilization, increased cardiac output.
- Left ventricular dilatation and hypertrophy – Heart failure
- Angina/myocardial infarction
- Impaired immune response.
- Growth retardation in children

An association between modest decline in hemoglobin level and progressive left ventricular growth has been shown in the patients who have early renal insufficiency [15]. There is decrease in left ventricular dimensions and an improvement in exercise capacity and cognitive functions due to partial correction of anemia.

HYPERTENSION AND CHRONIC KIDNEY DISEASE

Hypertension is a universal disease in all CKD patients and it is often manifested as an early sign of the disease. Hypertension is seen early in the course of CKD and is associated with left ventricular hypertrophy and accelerated progression of CKD to end stage renal disease. Hypertension can lead to the early development of cardiovascular disease in CKD. Cardiovascular disease is one of the main cause of increased morbidity and mortality. Thus we have to identify them at an earlier stage.

Hypertension in CKD patients is due to an: [8]

- Expanded extracellular volume and a diminished sodium excretion.
- Activation of renin –angiotensin– aldosterone system (RAAS) and the activation of sympathetic nervous system.
- Endothelial dysfunction
- Large artery stiffening

Patients with hypertension frequently have elevated serum uric acid levels and this may result in vascular damage contributing further to the development of hypertension in CKD.

Several prospective trials, like Multiple Risk Factor Intervention Trial (MRFIT)[16] and the systolic hypertension in elderly program, have shown a strong association between hypertension and rate of decline in kidney function and development of kidney failure. Analysis of National Health and Nutrition Evaluation Survey (NHANES) III data suggests that adequate BP control is achieved in only 11% of patients of CKD. More recent analysis of NHANES IV indicates that only 37% of hypertensive patients with CKD have BP controlled to a level of less than 130/80 mm Hg.

Risk factors for uncontrolled hypertension in CKD:

- Age more than 60
- Presence of albuminuria
- Associated other comorbid illness like diabetes, coronary artery disease and cerebrovascular accident.

Documentation of BP is important in the assessment of CKD because this is strongly associated with kidney disease progression and cardiovascular mortality. Treatment of hypertension in CKD should include specification of target blood pressure levels, non pharmacological therapies and specific anti-hypertensive agents.

Antihypertensive drugs reduce the albuminuria even in normotensive diabetic patients. Degree of blood pressure control appears to be an important factor in controlling the rate of progression of CKD.

The absence of hypertension in CKD may be due to: [13]

- Salt losing nephropathy – reflux nephropathy
    - interstitial nephropathies
    - post obstructive uropathy
    - medullary cystic disease
    - acute phase of acute tubular necrosis
- Anti-hypertensive therapy
- Volume depletion
- Poor left ventricular function

Low blood pressure actually carries a worse prognosis. This along with reduced body mass index and hypolipidemia shows advanced malnutrition – inflammation state.

CARDIOVASCULAR DISEASE AND CKD:

Cardiovascular disease is the most common cause of mortality in all stages of CKD. Age adjusted cardiovascular mortality is about 30 times higher in ESRD than in normal populations and more in dialysis patients. The risk is more in younger individuals with CKD. Most of the patients with CKD succumb to the cardiovascular disease even before they reach the end stage of renal disease. Hence all efforts of care should be given in the earlier stages of CKD to prevent the development of cardiovascular complications. [17]

Potential Mechanisms for Increased Cardiovascular Disease Risk in Chronic kidney disease [17]

1.	Chronic kidney disease is associated with an increase in prevalence of cardiovascular disease risk factors and these cardiovascular disease risk factors promote development and progression of CKD.
2.	Cardiovascular disease is a risk factor for CKD.
3.	Chronic kidney disease is an independent risk factor for cardiovascular disease.

The clinical consequences of cardiac disease in CKD are cardiomyopathy, ischemic vascular disease, left ventricular hypertrophy, myocardial ischemia and cardiac failure, valvular lesions (due to dystro

phic calcification of mitral and aortic valves). [18, 19, 20]

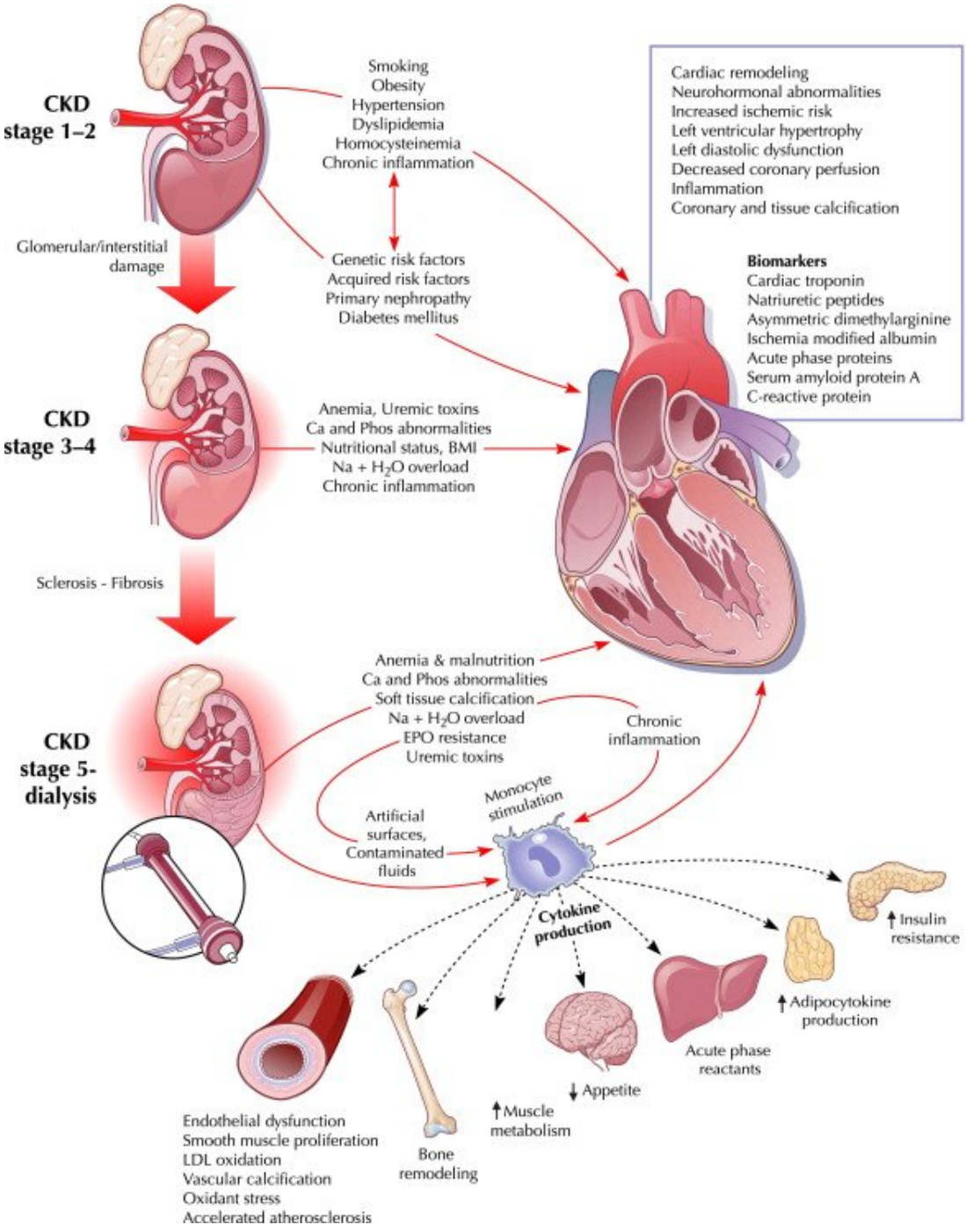
CARDIOVASCULAR DISEASE AND STAGE OF CKD:

Presentation with cardiovascular disease is influenced by the duration, severity and type of renal disease. LVH is already present in earlier stages of CKD. As the disease progresses; geometry of heart changes from concentric hypertrophy with normal LV volume; to eccentric hypertrophy with LV dilatation. Eventually LV growth and a decrease in myocardial contractility contribute to elevated LV pressures for a given volume, thus predisposing to heart failure. [21]

Manifestations of Cardiovascular Disease in CKD and Risk Factors

Pathology	Traditional Risk Factors	Non-traditional Risk Factors
Cardiomyopathy	Older age	Albuminuria
	Hypertension	Reduced glomerular filtration rate
	Valvular disease	Anemia
	Dyslipidemia	Inflammation
	Smoking	Arteriosclerosis
	Diabetes	Extracellular fluid volume overload
		Abnormal calcium/phosphate metabolism
Atherosclerosis	Older age	Albuminuria
	Male gender	Reduced glomerular filtration rate
	Hypertension	Anemia
	Diabetes	Inflammation
	Dyslipidemia	Oxidative stress
	Smoking	Endothelial dysfunction
	Physical inactivity	Homocysteine
	LVH	Lipoprotein (a)
		Malnutrition
		Thrombogenic factors
		Sympathetic activity
		Insulin resistance/metabolic syndrome
Arteriosclerosis	Older age	Albuminuria
	Male gender	Reduced glomerular filtration rate

Pathology	Traditional Risk Factors	Non-traditional Risk Factors
	Smoking	Endothelial dysfunction
	Hypertension	Abnormal calcium/phosphate metabolism
	Diabetes	Metabolic syndrome
	Dyslipidemia	


CKD stage 1–2
Smoking
Obesity
Hypertension
Dyslipidemia
Homocysteinemia
Chronic inflammation
Glomerular/interstitial damage
Genetic risk factors
Acquired risk factors
Primary nephropathy
Diabetes mellitus
Cardiac remodeling
Neurohormonal abnormalities
Increased ischemic risk
Left ventricular hypertrophy
Left diastolic dysfunction
Decreased coronary perfusion
Inflammation
Coronary and tissue calcification
Biomarkers
Cardiac troponin
Natriuretic peptides
Asymmetric dimethylarginine
Ischemia modified albumin
Acute phase proteins
Serum amyloid protein A
C-reactive protein
CKD stage 3–4
Anemia, Uremic toxins
Ca and Phos abnormalities
Nutritional status, BMI
Na + H2O overload
Chronic inflammation
Sclerosis - Fibrosis
CKD stage 5-dialysis
Anemia & malnutrition
Ca and Phos abnormalities
Soft tissue calcification
Na + H2O overload
EPO resistance
Uremic toxins
Chronic inflammation
Monocyte stimulation
Artificial surfaces, Contaminated fluids
Cytokine production
Insulin resistance
Adipocytokine production
Acute phase reactants
Appetite
Muscle metabolism
Bone remodeling
Endothelial dysfunction
Smooth muscle proliferation
LDL oxidation
Vascular calcification
Oxidant stress
Accelerated atherosclerosis

PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASE IN CKD

Heart failure and Atherosclerosis are more common in CKD patients thereby increasing the cardiovascular related mortality. Cardiovascular disease accelerates the progression of CKD and vice versa. In addition, CKD patients usually present with atypical symptoms making the diagnosis difficult.

Cardiomyopathy may present as an enlarged, dilated left ventricle with or without systolic dysfunction, or as a hypertrophic ventricle with normal left ventricular volume and diastolic dysfunction. Left ventricular disease is more common in CKD patients and is already present in about 85% patients of the patient starting on dialysis. Microvascular disease is also more common in CKD. Intramyocardial arterial wall thickening is the consistent finding independent of hypertension. It interferes with the perfusion reserve of the myocardium. There is also reduction in the capillary density interfering with myocardial blood and oxygen supply. Besides the anticipated accelerated atherosclerotic changes in the aorta, peripheral arteries and veins, calcification of the arterial media especially in the aorta leading to aortic stiffness, is an independent cardiovascular mortality.

The inflammatory state associated with CKD causes elevation of acute phase reactants due to the release of inflammatory cytokines like C-reactive protein. There is an accelerated vascular occlusive disease in the presence of inflammation and the associated low levels of Feutin with hyperphosphatemia permits more rapid vascular calcification. [13]

Thus, evaluation of a CKD patient should be properly investigated for the associated cardiovascular risk factors.

ISCHEMIC HEART DISEASE

Ischemic heart disease most results from atherosclerosis of the coronary arteries. Factors like hypertension, diabetes, and dyslipidemia accelerates atherosclerosis in CKD patients. Uremic state provides the hemodynamic, humoral, and metabolic abnormalities that induces endothelial cell activation and injury.

Coronary reserve is reduced in CKD caused because of marked left ventricular hypertrophy and microvascular disease. The episodes of recurrent hypotension and hypovolemia in haemodialysis patients may further aggravate coronary ischemia. Nitric oxide is reduced because of the elevated Asymmetric Di Methyl-Arginine (ADMA) augmenting the coronary ischemia. ADMA is the competitive inhibitor of nitric oxide synthase and is emerging as the strongest predictor of cardiovascular risk factor in ESRD. [21, 22]

LEFT VENTRICULAR HYPERTROPHY AND CKD [23]

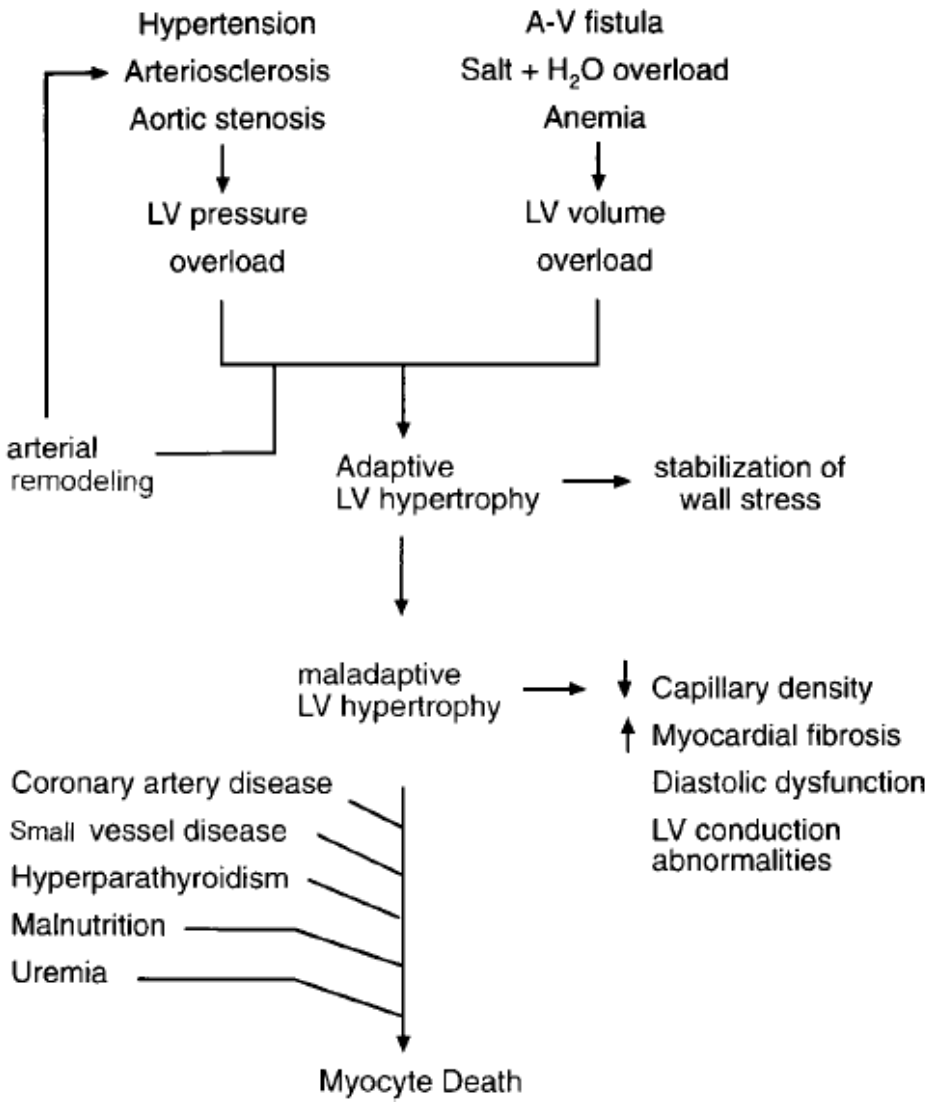
It is an adaptive remodelling process, which compensates for the increased work load with the aim of minimising ventricular wall stress.

- Pressure overload caused by increased afterload as in hypertension, arteriosclerosis, or aortic stenosis creates greater intracavitary pressure during ventricular contraction. This is achieved by arraying contractile proteins in parallel. As a result there is an increase in the wall thickness of interventricular septum and LV free (or "posterior" wall) and cavity volume remains normal. So that relative to the LV end diastolic diameter, wall thickness is increased. This is called as concentric hypertrophy. This leads to fall in diastolic compliance and there is a great risk of myocardial ischemia, even when there is no coronary artery disease. [22]

- In diseases like anemia, extracellular volume overload, and arteriovenous fistulas which causes volume overload, there is lengthening of contractile units this can lead into increase in the systolic stroke volume as described by Starling's law. Left ventricular dilatation produces increased wall tension, increased oxygen requirements and myocyte damage. Therefore decrease wall tension is brought about by wall thickening, left ventricular

dilatation and ventricular hypertrophy as secondary adaptations. This produces eccentric hypertrophy. [22]

The underlying molecular mechanisms are hypertrophy, apoptosis, and fibrosis that are influenced by growth factors, hormones, genetic factors and cytokines such as insulin like growth factor, angiotensin II, endothelin 1 and tumor necrosis factor alpha. Certain humoral factors like cardiac natriuretic peptide, troponin, homocysteine; asymmetric dimethyl arginine has also been implicated. [47]



Left ventricular (LV) pressure overload, LV volume overload and myocyte death in chronic uraemia [47]

Risk factors for left ventricular hypertrophy in patients with chronic renal insufficiency [47]

Not easily reversible	Easily Reversible
Older age Diabetes mellitus Abnormally stiff large Arteries	Arteriovenous connections Anaemia Hypertension Extracellular fluid volume expansion Uremic internal milieu Abnormalities of calcium phosphate homeostasis

Eventually LV hypertrophy becomes maladaptive; there is a resultant energy deficit. The electrophysiological abnormalities and maintenance of systolic efficiency occurs at the expense of impaired diastolic filling. Arrhythmias can occur due to conduction abnormalities secondary to fibrosis and due to prolongation of action potential from slower reuptake of calcium by sarcoplasmic reticulum. This along with fibrosis and increased LV stiffness contributes to diastolic dysfunction.

CONGESTIVE HEART FAILURE AND CKD:

The prevalence of heart failure increases with declining kidney function. It is the leading cause of mortality in CKD patients with higher mortality for diastolic than systolic failure.

Pathophysiology:

The mechanisms that causes LV failure in CKD

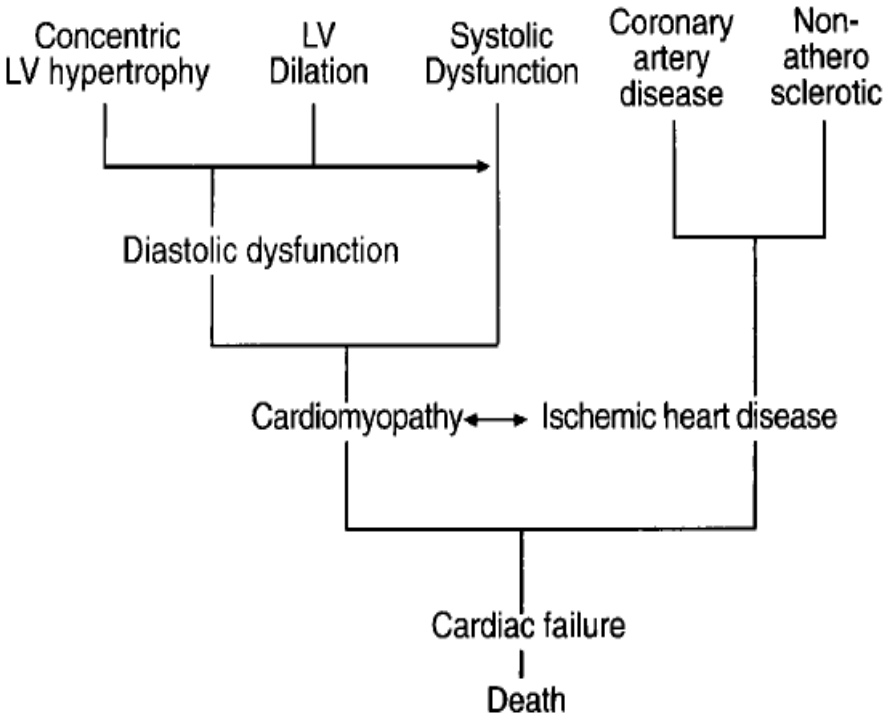
- ✓ pressure overload (due to hypertension and vascular stiffness),
- ✓ volume overload,
- ✓ CKD associated non hemodynamic factors

Catalytic iron dependent oxidative stress

Inappropriate activation of the renin-angiotensin system,

Inflammation

Stimulation of prohypertrophic and profibrogenic factors (transforming growth factor B , cardiotrophin-1, fibroblast growth factor-23, galectin-3) [48]



Pathophysiology of cardiomyopathy and ischemic heart disease in chronic uraemia [47]

Imbalance between increased collagen synthesis and decreased collagen degradation causes myocardial fibrosis which is responsible for LV stiffness, disturbances in diastolic filling and increased LV filling pressure which leads on to diastolic dysfunction.

The syndrome of heart failure is characterised by fatigue, effort intolerance and oedema. LVH, LV systolic and diastolic dysfunction can be diagnosed by Tissue Doppler Echocardiography imaging.

The current Kidney Disease Outcome Quality Initiative (KDOQI) guidelines recommend ECHO for all patients with stage 5 CKD, 1- 3 months after renal replacement therapy and 3 years thereafter, regardless of symptoms. However earlier screening and closer follow up may increase the prognostic value.

Prevention and treatment:

Prevention plays an important role in the progression of CKD. BP control and modification of the risk factors which causes CHF can help us to stop the further progression of the disease. Dietary salt restriction forms the mainstay of counselling. Intensive diuretic therapy is needed to treat the CHF as compared to CHF in a patient with normal kidney function. ACE Inhibitors, new direct renin inhibitors, ARBs and

mineralocorticoid receptor blockers are required for management of CHF in CKD. Recent studies suggest that these of carvedilol and bisoprolol in CKD with CHF. [48]

Other management strategies include

- Correction of anaemia (Hb> 10g/dl) reduces LVH. Intravenous iron and erythropoiesis stimulating agents shows us that it improves exercise tolerance but they have shown that there is no survival benefit.
- Minimising vascular calcification by control of calcium and phosphorus concentration – using non calcium containing phosphate binders , avoiding excessive low or high parathyroid hormone concentrations and adequate vitamin D status

Premature cardiovascular disease plays a significant role in the morbidity and mortality in CKD. ECHO is an excellent non-invasive method which can help us with the wall dimensions, details of anatomy of cardiac cavity and wall movement.

SYSTOLIC DYSFUNCTION

LVH is associated with both systolic and diastolic dysfunction. LVH is associated with systolic dysfunction expressed by decreased mid wall systolic fractional shortening and decreased ejection fraction. When there is a mild reduction in renal perfusion induced by slightly impaired LV systolic dysfunction, which is accompanied with pathological, highly pulsatile perfusion in kidney microvasculature might be mechanisms through which a progressive reduction of renal function takes place in patients with pre-existing renal damage. This renal insufficiency produced, affects cardiac function, producing a vicious cycle were the CKD can further decrease the cardiac function.

DIASTOLIC DYSFUNCTION

Diastolic dysfunction refers to a mechanical failure of the heart's chambers to fill properly with blood during the diastole phase of the cardiac cycle. This is caused by inadequate relaxation of the ventricles during diastole. Here the systolic function or the mechanical contraction of the heart is normal. Impairment of the diastolic phase can lead to inadequate filling of the left ventricle leads to a decrease in the amount of blood that is pumped out of the heart to oxygenate. In addition, if the ventricle does not fill with blood adequately, blood is drawn back into the atrium and eventually into the lungs, raising the pressure gradient of blood in the pulmonary vessels. This mismatched pressure gradient causes fluid or transudate to flow from these vessels into the lung alveoli, thereby causing pulmonary oedema.

The LV diastolic dysfunction appears to be the initial left ventricular dysfunction and might even preceed left ventricular hypertrophy. Diastolic heart function is influenced by numerous factors such as myocardial relaxation and compliance, transvalvular pressure gradient, heart rate, atrial contraction, preload, respiratory variant, the restraint of pericardium and thoracic wall, as well as arrhythmias and valve incompetence. The abnormal ventricular filling in uraemia results increased LV stiffness caused by intramyocardial fibrosis and associated

delayed relaxation. By virtue of an increase in LV stiffness, small changes in LV volume results in large changes in LV pressures, thus predisposing to symptomatic pulmonary oedema. Sometimes volume depletion can result in a large fall in LV pressure with symptomatic hypotension and hemodynamic instability.

Hypertension, anaemia and alteration in fluid and electrolyte balance are identified as major determinants of LVH in CKD. However beyond hemodynamic factors, inappropriate activation of RAAS, inflammation, oxidative stress, collagen and muscle growth plays a role. Impairment of diastolic dysfunction can occur early, even in the absence of LVH. So early detection of LV dysfunction in CKD could lead to an improvement in CV outcomes in CKD. [23]

Although patients with CKD have high traditional risk factors, this isn't fully responsible for CV mortality [27]. Other factors such as:

- ✓ secondary hyperparathyroidism ,
- ✓ changes in mineral metabolism
- ✓ Impaired clearance of some growth factors. The carboxy terminal peptide of collagen type 1 (PICP) or

cardiotrophin- 1 (CT-1) were elevated in CKD patients than those with normal function.

- ✓ osteoblasts and osteophytes secretes FGF 23, which maintains serum phosphate concentrations in CKD by stimulating phosphorus excretion and decreasing dietary phosphorus absorption through inhibition of 1, 25OH vitamin D synthesis. [39, 40, 41, 42]. This increased concentrations of FGF 23 in CKD patients induces fibrosis. This increased myocardial fibrosis has a central role in diastolic dysfunction.
- ✓ There is also a role for inflammation in diastolic dysfunction as demonstrated by increased CRP. [50]

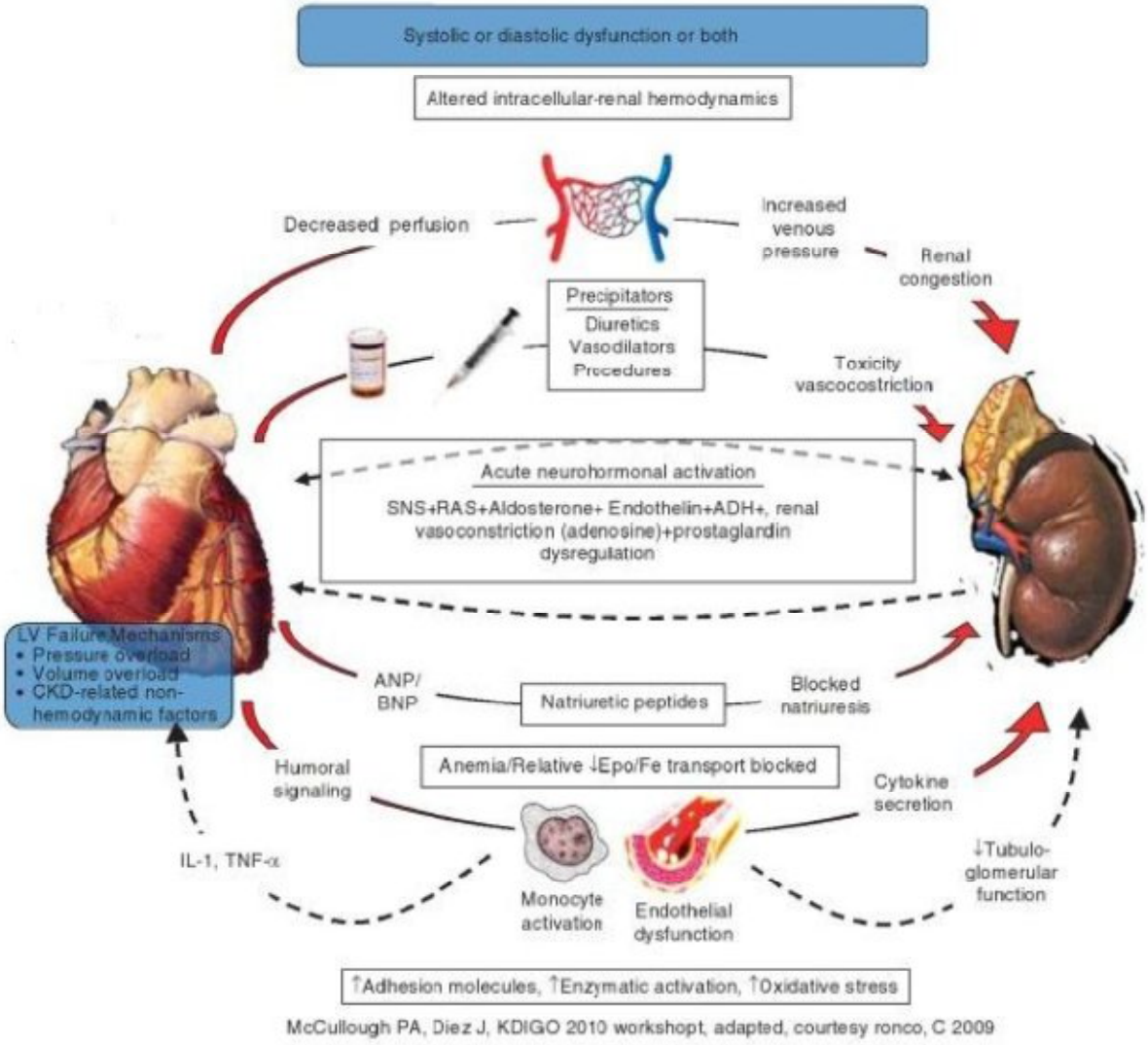
Grading of diastolic dysfunction:

- Grade I –Inversion of ratio of peak early to peak atrial velocity – curve, with reduced early ventricular filling, due to reduced ventricular relaxation

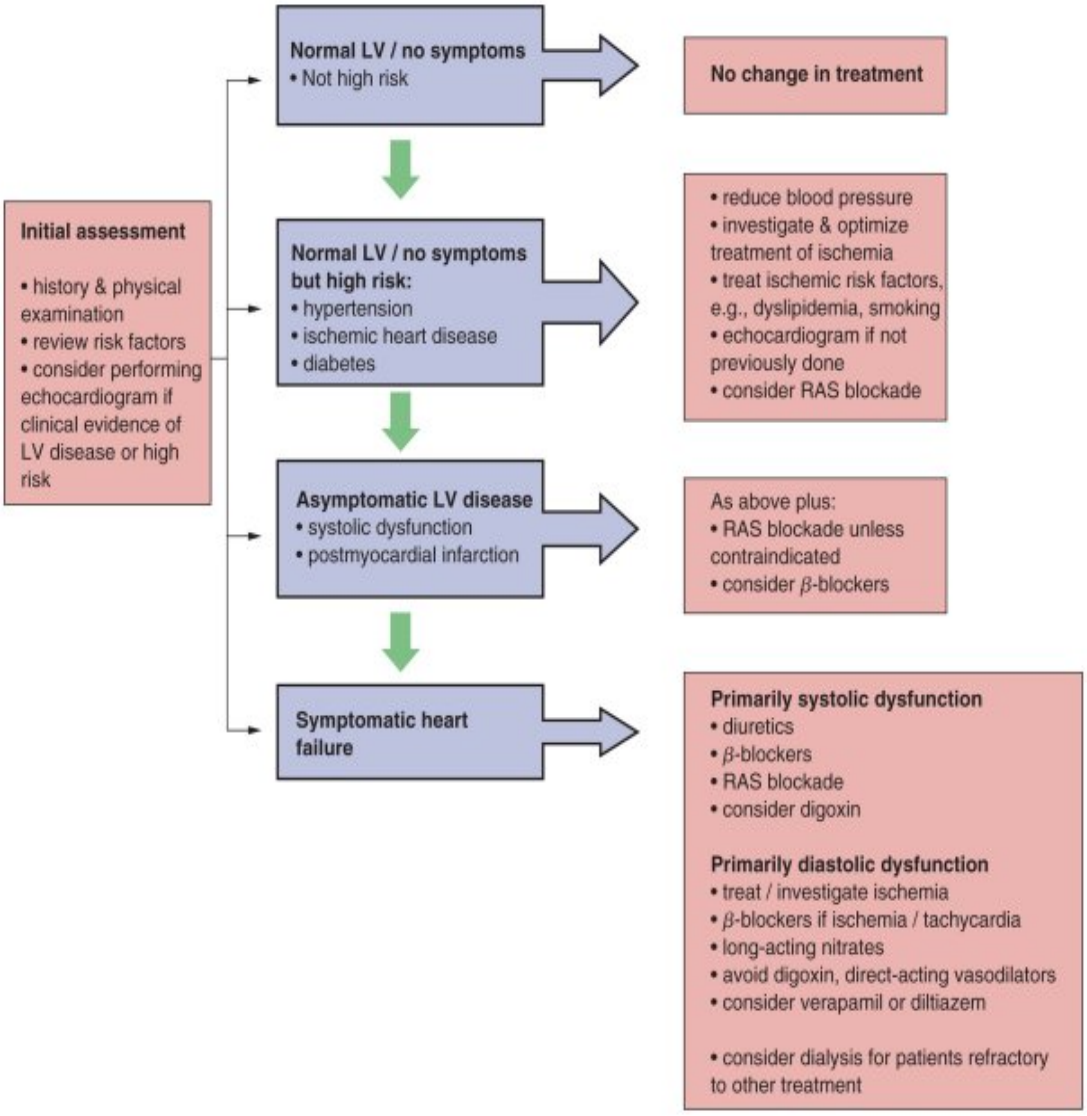
This is the mildest form of diastolic heart failure. Patients are usually asymptomatic. Grade 1 = impaired relaxation pattern

with normal filling pressure. Grade 1a = impaired relaxation pattern with increased filling pressure

- Grade II –Pseudonormalisation of E/A flow pattern, due to increased atrial and ventricular filling pressures and decreased ventricular relaxation.
- Grade III – This is a severe form of diastolic dysfunction characterized by restrictive filling of the heart that leads to symptoms of advanced heart failure. When the patient is asked to perform the Valsalva maneuver during echocardiography, the diastolic abnormalities seem to reverse. This grade III dysfunction is therefore also called reversible restrictive diastolic dysfunction.
- Grade IV – This is also a severe form diastolic dysfunction characterized by restrictive filling. However, at this stage, the abnormalities are not reversible and grade IV diastolic dysfunction is also called “fixed restrictive diastolic dysfunction”.



Pathophysiology of cardiovascular dysfunction in CKD



Approach to treatment of left ventricular disorders and cardiac failure in patients with chronic kidney disease. [17]

VALVULAR CALCIFICATION[13]

- Valvular lesions in CKD are acquired and are due to dystrophic calcification. Aortic and mitral valves (annulus and leaflets) are commonly involved. Aortic valve stenosis evolves from valve sclerosis and is associated with increased cardiovascular mortality.
- Risk factors associated are age, duration of dialysis, hyperphosphatemia, and elevated calcium phosphate product.[13]

PERICARDIAL DISEASE:

Pericarditis is very common. It is an absolute indication for dialysis. Sometimes it is associated with pericardial effusion

GLOMERULAR FILTRATION RATE [7]

GFR is the primary metric for kidney function and its direct measurement involves administration of inulin or iothalamate a radioactive isotope that can be filtered at the glomerulus but neither secreted nor absorbed.

Serum creatinine is a useful marker to estimate the level of GFR. However serum creatinine is not an ideal marker of GFR, because it is both filtered at the glomerulus and secreted by the proximal tubules. GFR is related directly to the urine creatinine and inversely to the serum creatinine (Ucr / Up). The estimated GFR using the following methods are superior for the assessment of renal function:

1) MDRD (Modification of Diet in Renal Disease study) equation :

$$eGFR(ml / min / 1.73\ m^2) = 186.3 \times (\text{Plasma creatinine})^{-1.154} \times (age)^{-0.203}$$

x 0.742 if female

x 1.21 if African American

2) Cockcroft-Gault equation :

This equation was used to predict creatinine clearance (CrCl), but has been used to estimate GFR

$$\text{CrCl or eGFR} = \frac{(140\text{-age}) \times (\text{Body weight in Kg})}{(\text{Serum creatinine}) \times (72)} \times 0.85 \text{ if female}$$

- **CKD – EPI eGFR** = 141 x min (S. creatinine / k, 1)a x max

MDRD equation has poorer accuracy when GFR > 60 ml / min / 1.73 m^2

The chronic use of glucocorticoids, gradual loss of muscle mass due to chronic illness or malnutrition can mask significant changes in GFR.

PROTEINURIA:

Proteinuria is the most important early indicator of kidney damage. The gold standard test for evaluation of albuminuria is the measurement of 24 hour urine protein. The measurement of albumin to creatinine ratio in spot first void urine is a better method in practice.

ASSESSMENT OF PROTEIURIA

	Urine collection method	Normal	Micro albuminuria	Albuminuria or clinical proteinuria
Total protein	24-hour urine protein	< 300 mg/dl	--	>300 mg/dl
	Spot urine protein/creatinine ratio	< 200 mg/g	--	> 200 mg/g
Albumin	24-hour excretion	< 30 mg/day	30-300mg/day	>300 mg/day
	Spot albumin specific dipstick	<3 mg/dl	>3 mg/dl	--
	Spot urine albumin/creatinine ratio	<17 mg/g for men. <25 mg/g for women.	17-250 mg/g for men. 25-355 mg/g for women.	>250 mg/g for men. >355 mg/g for women

ECHOCARDIOGRAPHY AND CKD

M mode and two dimensional echocardiography provides us with a non-invasive and cheap procedure to assess the left ventricular structure and function. They also help us in the imaging of valves and pericardium. Systolic dysfunction can be diagnosed by measuring ejection fraction or low fractional shortening. You can also use ECHO to look at the LVH and LV geometry. The degree of hypertrophy can calculated by measuring the LV mass index or increased thickness of LV wall.

Diastolic LV function can be measured by Doppler analysis when flow in the mitral valve during diastole. When the mitral valve opens there is ventricular relaxation which leads to sudden increase in flow measured as E ('early') peak. This is followed later by increase in the A ('atrial') peak, which reflects the atrial contraction. By assuming that the atrial function is normal, the increased stiffness of the LV due to LVH as in CKD, leads to smaller E peak and a bigger A peak, expressed as decreased E/A ratio.

Dobutamine stress echocardiography can be used in CKD patients for screening for ischaemic heart disease. It can also be used to determine the systolic reserve in patients with impaired systolic function or valvular heart disease.

MATERIALS AND METHODS

STUDY POPULATION:

This study is to be conducted among 100 established CKD patients who are admitted in Govt. Rajaji Hospital, Madurai in the General Medicine and Nephrology Departments and 50 age and sex matched controls. Out of the 100 CKD patients, 50 will be hypertensive and 50 will be normotensive CKD patients.

Cases were classified into different stages of Chronic Kidney Disease based on estimated Glomerular filtration rate (eGFR). eGFR was calculated using MDRD formula.

MDRD (Modification of Diet Renal Disease study) equation :

$$eGFR(ml / min / 1.73\ m^2) = 186.3 \times (\text{Plasma creatinine})^{-1.154} \times (age)^{-0.203}$$

x 0.742 if female

INCLUSION CRITERIA:

- Age > 18 years, both sex, with established Chronic Kidney Disease

  i.e.: Symptoms and signs of renal disease > 3 months

  Proteinuria > 1g/dl

  Ultrasonography showing kidney size < 8.5 cm

  Reduced creatinine clearance (eGFR) pointing to CKD

- Those who have not received any forms of renal replacement therapy.
- 50 hypertensive (BP > 140/90) and 50 normotensive CKD patients in whom the duration of CKD is matched.
- 50 sex and age matched healthy individuals as controls.

EXCLUSION CRITERIA:

- Age < 18 years and > 70 years
- Patients with Acute Kidney Injury
- Patients with history and clinical features suggestive of pre-existing cardiac diseases like rheumatic valvular heart disease, congenital heart disease, coronary heart disease, cardiomyopathy and pericardial diseases.
- Patients on dialysis and kidney transplant patients
- Patients who are diabetic

ANTICIPATED OUTCOME:

1. There is LV dysfunction both systolic and or diastolic in CKD patients as compared to controls.
2. Diastolic dysfunction is first to appear in CKD patients and will be present in more number of patients as compared to systolic dysfunction.
3. Lower the eGFR more severe will be the LV dysfunction
4. CKD patients with hypertension and anemia will have more severe LV dysfunction.

DATA COLLECTION:

A previously designed proforma will be used to collect the demographic and clinical details of the patients and controls. A thorough clinical examination will be done. An ECG and an Ultrasound Abdomen will be taken.

Blood investigations taken. Echocardiography will be taken according to the standard guidelines. All measurements were made following American Society of Echocardiography (ASE) recommendations.

- ✓ Patients with EF < 50% were accepted as having LV systolic dysfunction
- ✓ Diastolic dysfunction was graded according to the ratio of transmitral early (E) and late (A) flow velocities (E/A ratio)

E/A ratio <0.8 – Grade1

0.8 – 1.5 – Grade 2

>2 – Grade 3

LABORATARY INVESTIGATIONS:

Blood samples were collected from all participants to estimate Haemoglobin. Blood urea, and Serum creatinine. Urine sample will be analysed for albuminuria.

DATA ANALYSIS:

The final data was entered onto Microsoft excel sheet 2010 and statistical analysis was done using SPSS software. The statistical tools applied were median, mean, standard deviation , Pearson's correlation and chi – square test coefficient. These results are considered very significant when the p value < 0.001 and significant if p value < 0.05

DESIGN OF STUDY: Cross sectional analytical study.

PERIOD OF STUDY: May 2013 to August 2014

COLLABORATING DEPARTMENTS:

Department of General Medicine,

Department of Nephrology,

Department of Cardiology,

Department of Radiology,

Department of Biochemistry.

ETHICAL CLEARANCE: Obtained

CONSENT **:** Individual written and informed consent.

ANALYSIS **:** Statistical analysis – Chi square,

Pearson's correlation coefficient

CONFLICT OF INTEREST : NIL

FINANCIAL SUPPORT **:** NIL

OBSERVATION AND RESULTS

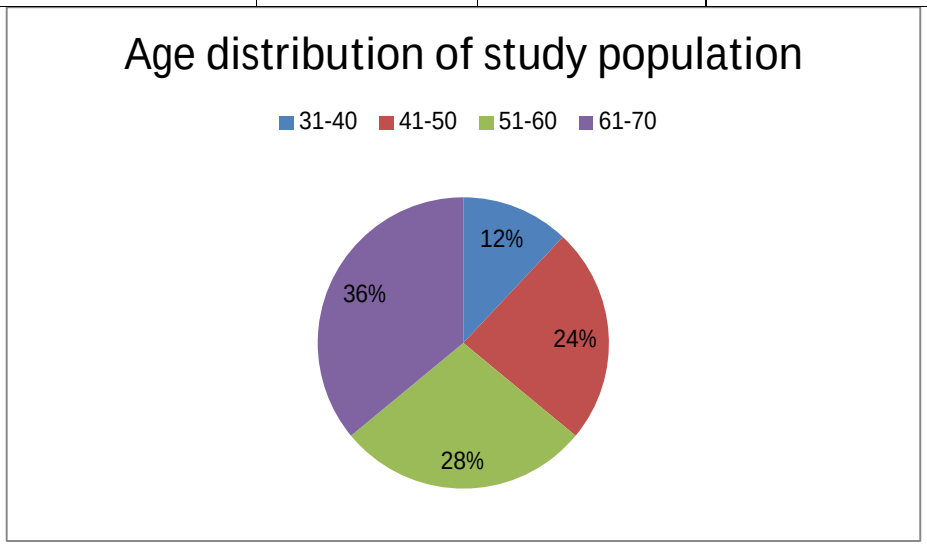
TABLE 1: PARAMETERS OF PARTICIPANT GROUPS

	CKD + HTN (n=50)	**CKD + NT (n=50)**	**CONTROLS (n=50)**
Age	54.12±13.06	54.64±14.72	54.06±12.59
Sex : Male Female	35 15	35 15	35 15
BP (mm Hg) Systolic Diastolic	 160±10.2 102±6.2	 126±6.8 82±4.6	 116±6.2 76±3.8
Body weight	52.96±9.92	51.82±11.37	56.52±11.73
BMI	21.95±4.22	21.68±3.96	22.85±4.5
eGFR (ml/min/1.73m2)	14.59±13	22.21±13.31	95.27±17.04
S.creatinine(mg/dl)	7.44±5.35	3.77±1.78	0.83±0.16
Hb%	7.39±2.40	7.72±1.56	12.85±2.02
LVEF	50.68±10.41	53.98±9.19	55.6±9.02
Diastolic dysfunction	1.75±0.75	1.57±0.89	0.81±0.28

TABLE 2

AGE DISTRIBUTION OF THE STUDY POPULATION

AGE GROUP	CKD + HTN (n = 50)	CKD + NT (n= 50)	CONTROLS (n = 50)
31-40	6	6	6
41-50	12	12	12
51-60	14	14	14
61-70	18	18	18



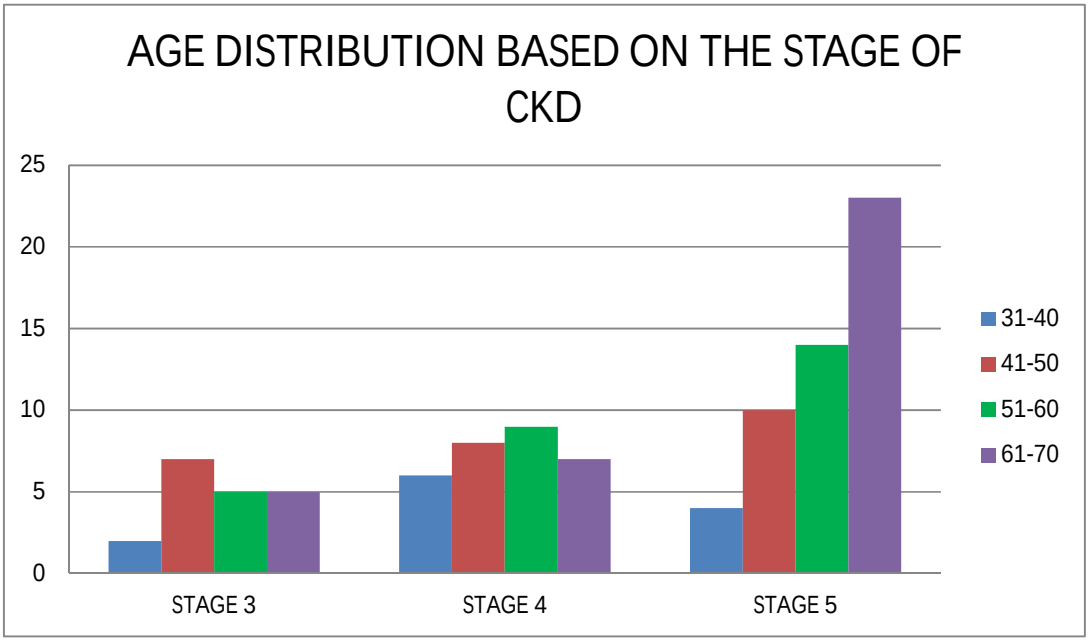
Mean age (± S.D): 54.12±13.06 years, minimum: 32 years, maximum: 70 years.

About 52% of study subjects were in the age group of 41-60 years while 36% were aged 61-70 years.

TABLE 3

AGE DISTRIBUTION BASED ON THE STAGE OF CKD

STAGES	AGE 31-40	AGE 41-50	AGE 51-60	AGE 61-70
STAGE 3	2	7	5	5
STAGE 4	6	8	9	7
STAGE 5	4	10	14	23

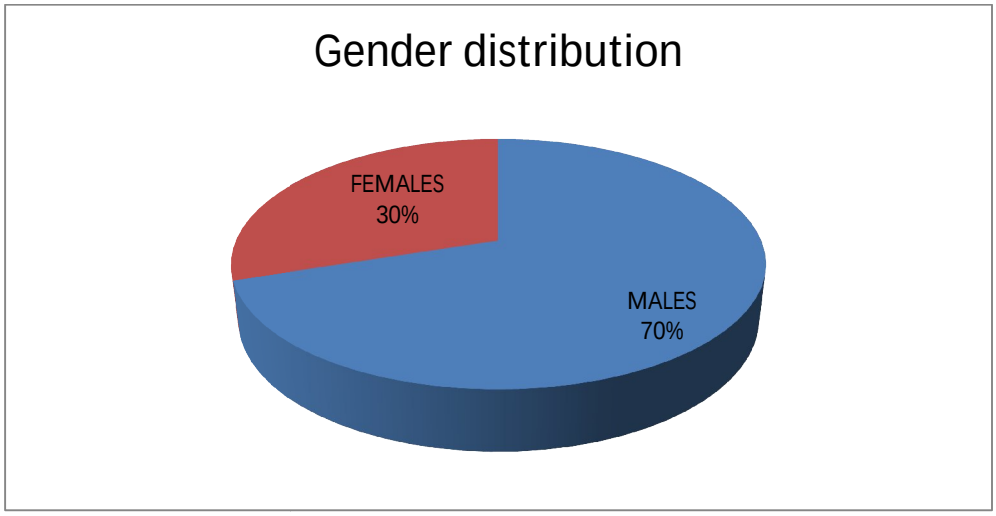


As age advances, stage of CKD also increases.

TABLE 4

GENDER DISTRIBUTION

GENDER	CKD + HTN (n = 50)	CKD + NT (n = 50)	CONTROLS (n = 50)
MALE	35	35	35
FEMALE	15	15	15

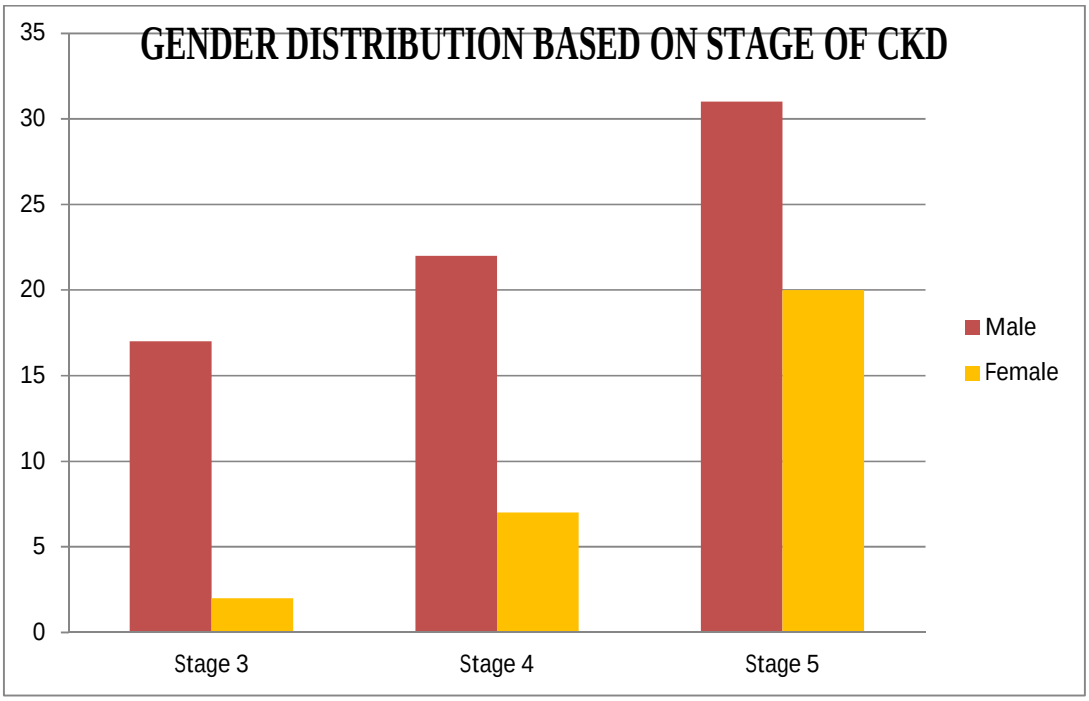


Majority of the study subjects were males (70%) while the remaining 30% were females.

TABLE 5

GENDER DISTRIBUTION BASED ON STAGE OF CKD (n = 100)

STAGE	MALE	FEMALE
STAGE 3	17	2
STAGE 4	22	7
STAGE 5	31	20

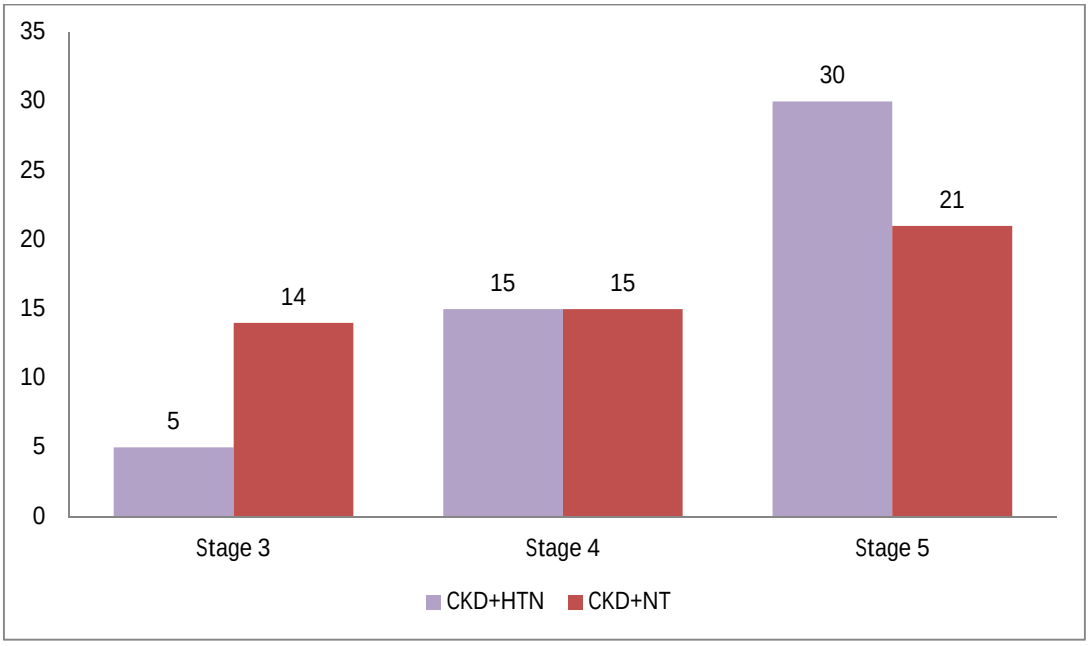


In all stages of CKD, males have a higher prevalence than females.

TABLE 6

DISTRIBUTION OF STUDY GROUP ACCORDING TO STAGE OF CKD

STAGE	CKD + HTN (n = 50)	CKD + NT (n = 50)
3	5	14
4	15	15
5	30	21

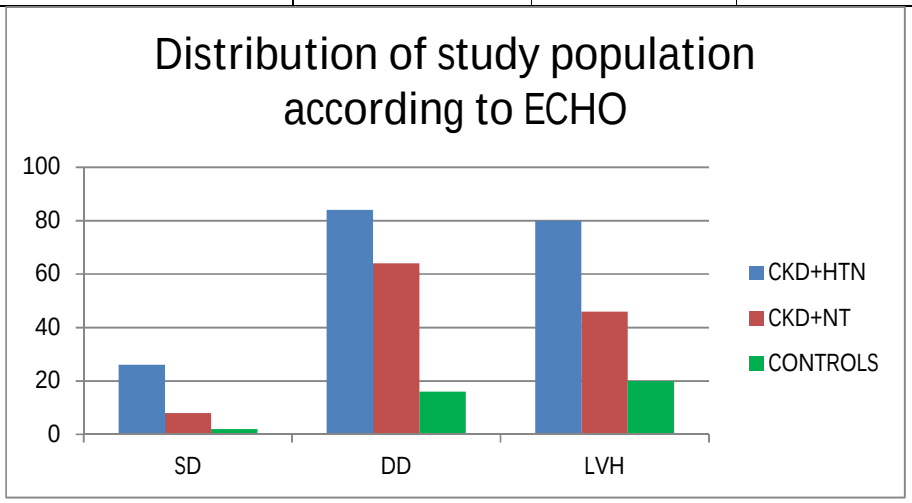


Stage 5 CKD has a higher number of hypertensives (30%)

TABLE 7

DISTRIBUTION OF STUDY POPULATION ACCORDING TO ECHOCARDIOGRAM

	CKD+HTN (n=50)	CKD + NT (n=50)	CONTROLS (n=50)
SYSTOLIC DYSFUNCTION(SD)	13(26%)	4(8%)	1(2%)
DIASTOLIC DYSFUNCTION(DD)	42(84%)	32(64%)	8(16%)
LVH	40(80%)	23(46%)	10(20%)



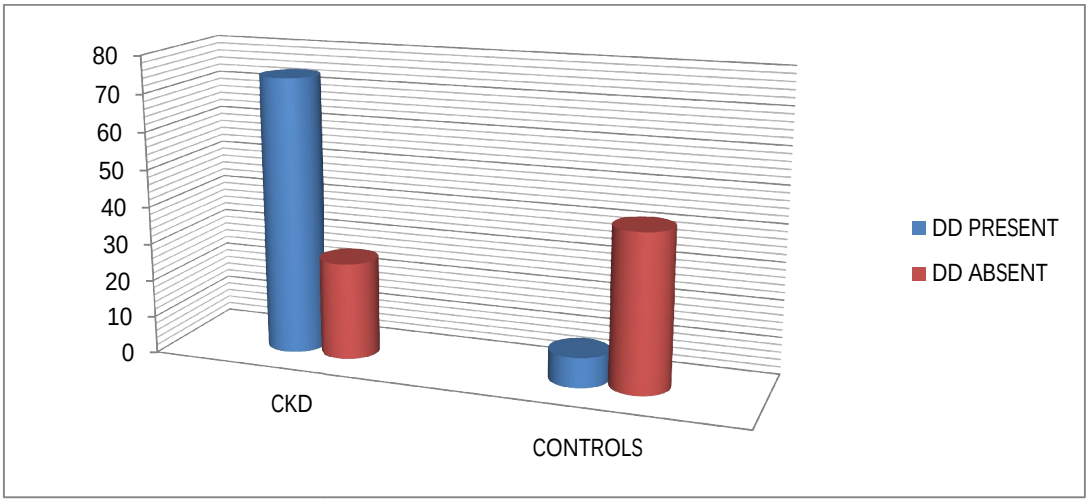
84% of CKD with hypertension had diastolic dysfunction, while only 26% of the same group had systolic dysfunction. In CKD with normotension 64% had diastolic dysfunction, whereas only 8% had systolic dysfunction.

TABLE 8

PREVALENCE OF LV DIASTOLIC DYSFUNCTION IN CKD

	DD PRESENT	DD ABSENT	TOTAL
CKD	74	26	100
CONTROLS	8	42	50
TOTAL	82	68	150

Chi square p value < 0.0001



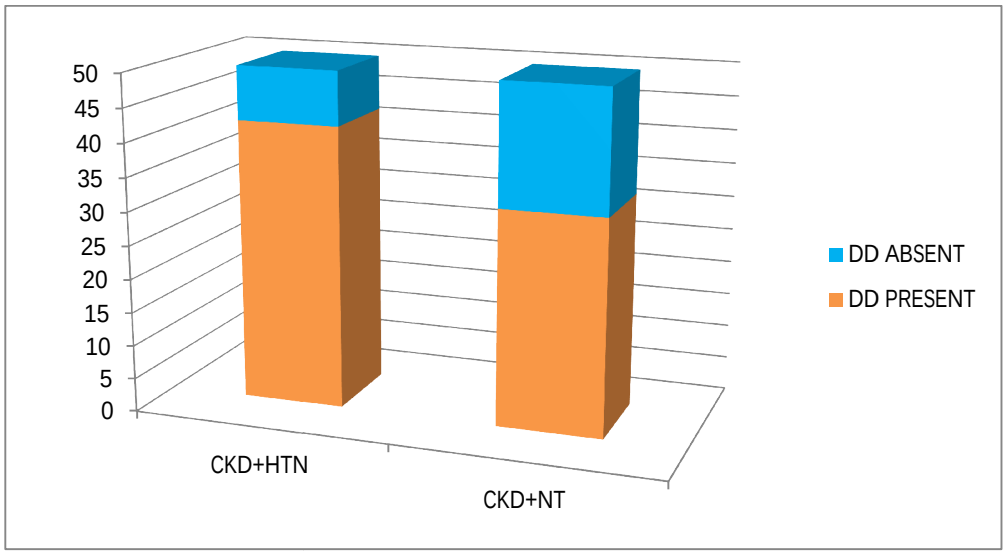
74% of CKD patients have diastolic dysfunction as compared to 16% in controls. This association was found to be extremely significant by Chi square test.

TABLE 9

COMPARISON OF DIASTOLIC DYSFUNCTION IN CKD + HTN AND CKD + NT

	DD PRESENT	DD ABSENT	TOTAL
CKD + HTN	42	8	50
CKD + NT	32	18	50
TOTAL	64	26	100

Chi square p value = 0.022



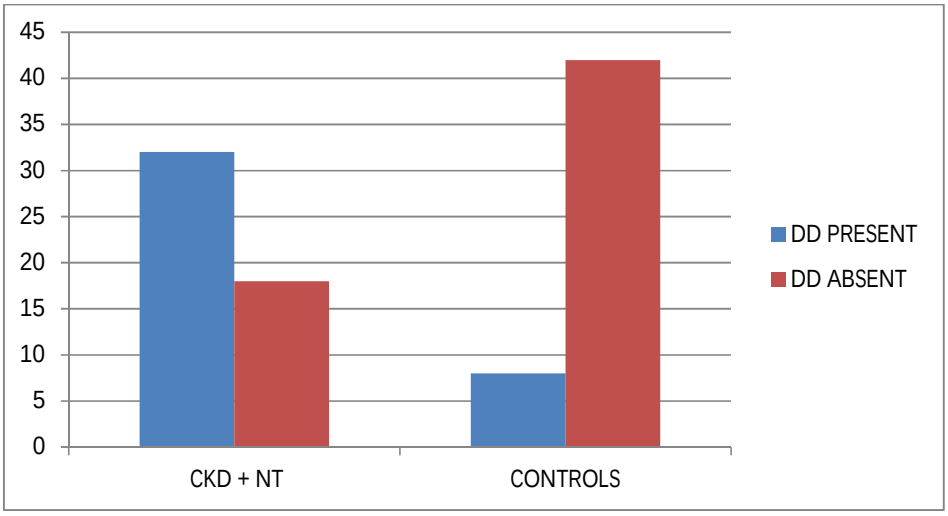
84% of CKD with hypertension have diastolic dysfunction as compared to 64% in CKD normontensives. This association was found to be statistically significant.

TABLE 10

COMPARISON OF DIASTOLIC DYSFUNCTION IN CKD + NT AS COMPARED TO CONTROLS

	DD PRESENT	DD ABSENT	TOTAL
CKD + NT	32	18	50
CONTROLS	8	42	50
TOTAL	40	60	100

Chi square p value < 0.05

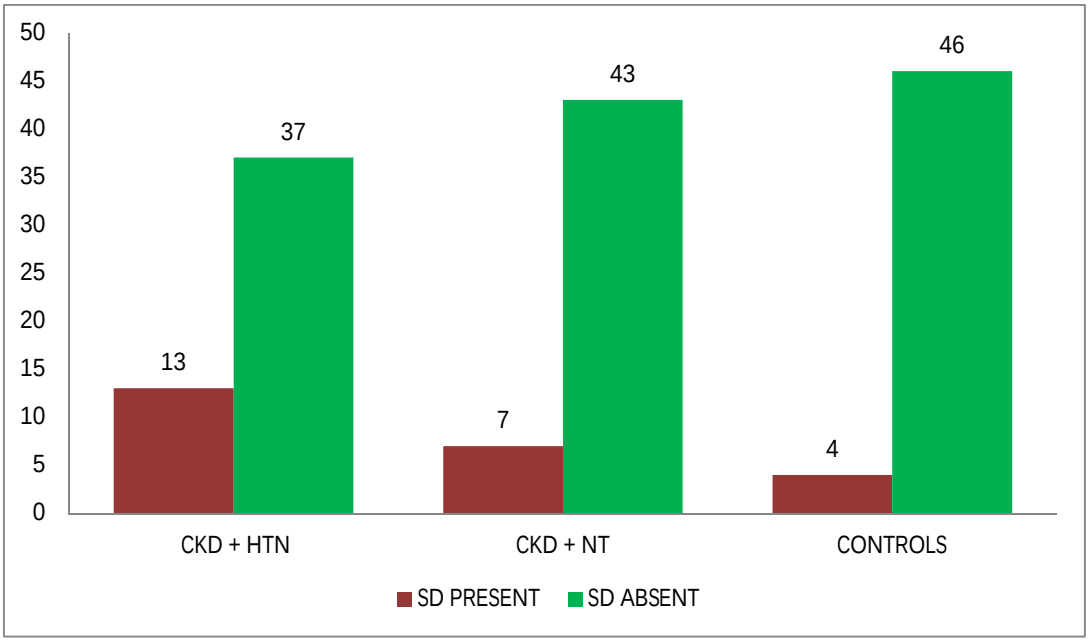


64% of CKD with normotension have diastolic dysfunction as compared to 16% in controls. This association was found to be statistically significant.

TABLE 11

PREVALENCE OF SYSTOLIC DYSFUNCTION IN CKD

	SD PRESENT	SD ABSENT	TOTAL
CKD + HTN	13	37	50
CKD + NT	4	46	50
CONTROLS	1	49	50

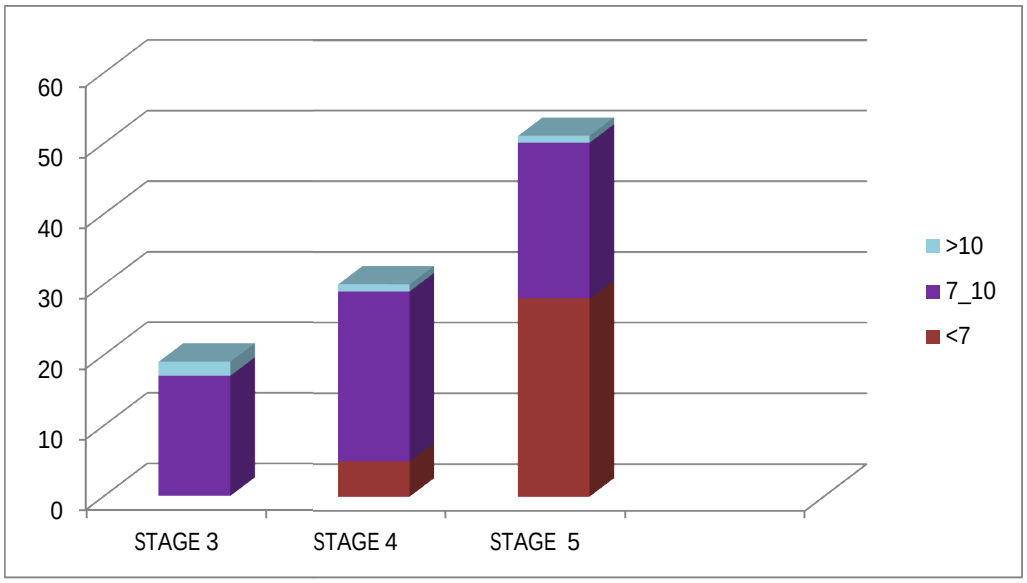


26% of CKD with hypertensives and 8% of CKD normotensives had systolic dysfunction. This was found to be statistically significant, but when CKD normotensives were compared with that of controls, this association was found to be not significant.

TABLE 12

PREVALENCE OF ANAEMIA IN STUDY GROUP (n=100)

STAGE	Hb <7 gm/dl	Hb 7-10 gm/dl	Hb >10 gm/dl
STAGE 3	0	17	2
STAGE 4	5	24	1
STAGE 5	28	22	1

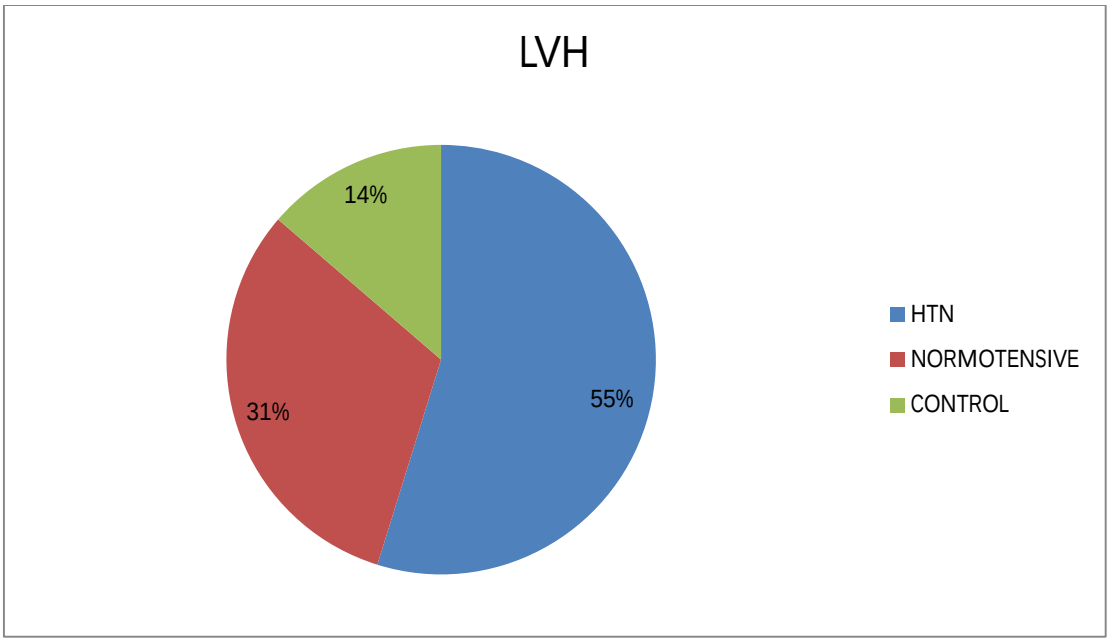


There is a higher prevalence of anaemia as CKD progresses. Hb was found to be > 7 gm/dl in all CKD patients in stage 3 and < 7gm/dl in 28 CKD patients in stage 5.

TABLE 13

DISTRIBUTION OF LVH (n = 70)

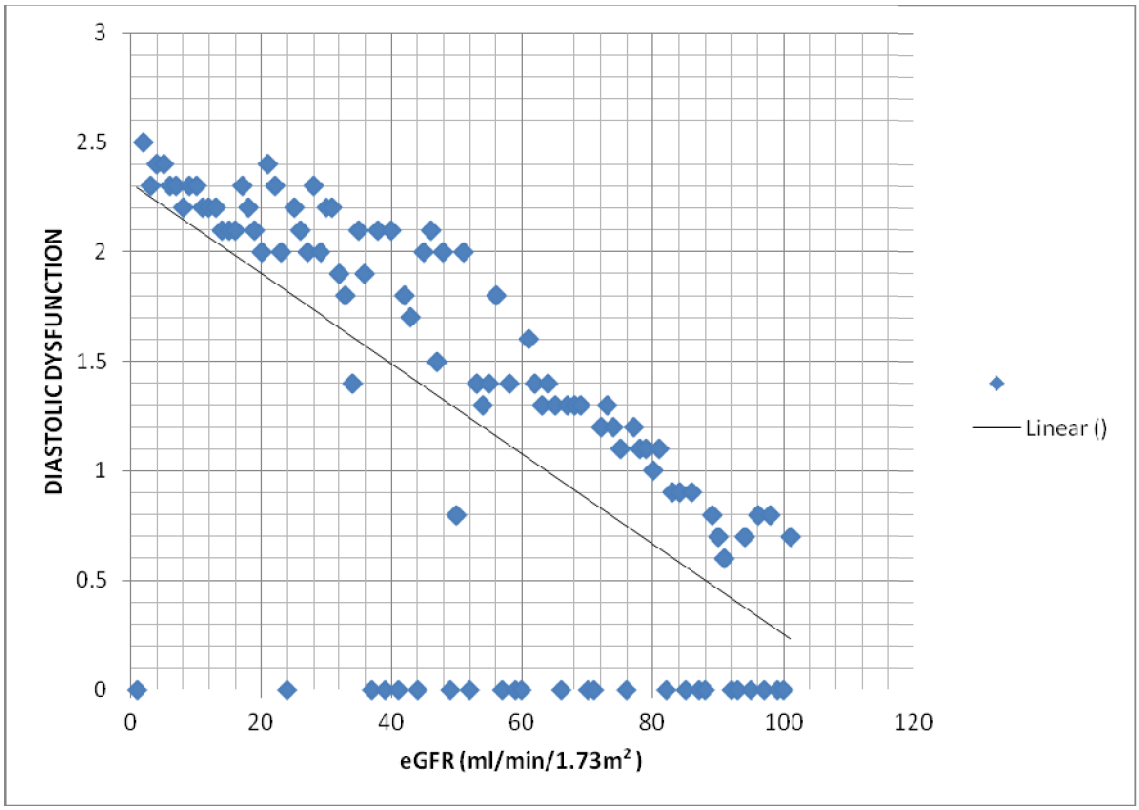
	CKD + HTN	CKD + NT	CONTROLS
LVH	**40**	**20**	**10**



In patients with LVH 55% of them were CKD hypertensives compared to 31% were CKD normotensives.

TABLE 14

CORRELATION BETWEEN eGFR AND DIASTOLIC DYSFUNCTION



According to Pearson's correlation coefficient; the correlation between eGFR and diastolic dysfunction was calculated and R value obtained was R= - 0.90682. This showed that there is a moderate negative correlation between eGFR and diastolic dysfunction. That is as the eGFR decreases, the diastolic dysfunction increases.

DISCUSSION

Various epidemiological studies show that a moderate reduction in kidney function is associated with increased cardiovascular risk, and that the level of kidney function is an independent predictor of cardiovascular outcome [24, 25, 26]

The main aim of the study was to demonstrate the prevalence of left ventricular dysfunction in CKD as compared to that of controls and its correlation with the eGFR.

The association of various parameters like sex, age, BMI, LVH was also studied.

In this study, the study participants were divided into three groups. 50 hypertensive CKD patients, 50 normotensive CKD patients and 50 controls being age and sex matched.

It was observed that there was a declining trend in eGFR and Hb with the progression of renal failure, while there was an ascending trend with systolic and diastolic blood pressure and serum creatinine.

Age distribution in study population:

The mean age group of the study population was 54.12±13.06 years. The minimum age was 32 years and the maximum age was 70

years. About 52% of study subjects were in the age group of 41 - 60 years, while 36 % were aged between 61 – 70 years. Thus we have shown in our study that the prevalence of CKD is most prevalent in 4th – 6th decade. In India, CKD is reported within the mean age of 50 years. In SEEK study; CKD has a mean age group of 45 years.[5]

Sex distribution in study population:

In my study, 70 % of CKD patients were males, and 30% CKD patients were females. This shows that CKD is more common in males than in females. This is in accordance to the SEEK study [5], where males showed a higher prevalence than females. The Indian CKD registry [6] show that the CKD male: female ratio was 70: 30. The age and gender distribution of the population in both the study and control groups were almost equal and were comparable.

Blood pressure in study population:

The mean systolic BP was 160±10.2 mm Hg in hypertensive group and 126±6.8 mm Hg in normotensive group. The mean diastolic BP was 108±6.2 mm Hg in hypertensive and 82±4.6 mm Hg in normotensive group. The mean systolic BP in the controls was 116±2.9 mm Hg and mean diastolic BP was 75.5±3.8 mm Hg.

Anaemia in study population:

In this study, CKD patients had significant anaemia with mean haemoglobin of about 7.39±2.40 gm/dl in CKD hypertensive group, 7.72±1.56 gm/dl in CKD normotensive group and 12.85±2.0 gm/dl in controls. There was not much of a difference between the CKD hypertensive and normotensive group; although a better haemoglobin value was expected in the normotensive patients.

Serum creatinine and eGFR values:

The average Serum creatinine values in CKD hypertensives, CKD normotensives and controls are 7.44±5.35, 3.77±1.7 and 0.83±0.16. The average eGFR values in CKD hypertensives, CKD normotensives and control groups are 14.59 ± 13, 22.21 ± 13.31 and 95.27 ± 17.04 mg/dl. This shows that CKD hypertensives have a very low eGFR as compared to that of controls.

Left ventricular Hypertrophy:

In my study 55% of patients with LVH were CKD hypertensives as compared to 31% were CKD normotensives. This is in accordance with the study done by Levin et al which showed that 70% of ESRD patients had LVH [(35)] and Paoletti et al 74% had LVH [(36)]

LV systolic dysfunction:

26% of CKD with hypertensives and 8% of CKD normotensives had systolic dysfunction. This was found to be statistically significant, but when CKD normotensives were compared with that of controls, this association was found to be not significant. This is similar to the study conducted by Shah Harsh D et al, Raj et al and P. Dangri et al.[19] This suggests that LVEF is well maintained till late. This shows that when the ventricle is stressed by a haemodynamic overload, it first uses its compensatory mechanism to maintain normal performance. Its only when all these compensatory mechanisms have been maximally used that there is a decline in ejection phase indices.

LV diastolic dysfunction:

74% of CKD patients have diastolic dysfunction as compared to 16% in controls. This association was found to be extremely significant by Chi square test. (p value <0.0001)

The average E/A ratio in CKD hypertensives were 1.75 ± 0.75. According to Virtenen et al, in Grade 5 CKD, the mean E/A ratio is1.5 ± 0.5. [31].In my study, 84% of CKD with hypertension have diastolic dysfunction as compared to 64% in CKD normontensives. This association was found to be statistically significant. (p value = 0.02)

The average E/A ratio in CKD normotensives were 1.57 ± 0.89. 64% of CKD with normotension have diastolic dysfunction as compared to 16% in controls. This association was found to be statistically significant. (p value <0.05)

It was found during the study that, among the control group 8 out of 50 has E/A ratio less than 1.These were people who were above 60 years and here diastolic dysfunction was considered physiological.

This study shows that there is a statistically significant occurrence of diastolic dysfunction in CKD with normotensives as compared to that of control. This proves that it is not the hemodynamic risk factors such as hypertension and anaemia alone that contributes to LVH and LV dysfunction. The uraemia related risk factors also plays a role. So management should be aimed at not only hypertension and anaemia but also control of uraemia related risk factors.

LV diastolic dysfunction is frequent among CKD patients and may produce heart failure and mortality. It has been reported that in ESRD, diastolic dysfunction deteriorates in parallel with LVH. [43, 44] The negative outcome is stronger in patients with diastolic failure. [45] Diastolic dysfunction in CKD may occur early even in the absence of LVH [46]

According to Pearson's correlation coefficient; the correlation between eGFR and diastolic dysfunction was calculated and R value obtained was R= - 0.90682

This showed that there is a moderate negative correlation between eGFR and diastolic dysfunction. That is as the eGFR decreases, the diastolic dysfunction increases.

To conclude, patients with CKD have higher prevalence of diastolic and systolic dysfunction and the diastolic dysfunction antedates the systolic dysfunction. [50, 51, 52, 53, 54]

SUMMARY

The main aim of the study was to demonstrate the prevalence of left ventricular dysfunction in CKD as compared to that of controls and its correlation with the eGFR.

The mean age group of the study population was 54.12±13.06 years. In my study, 70 % of CKD patients were males, and 30% CKD patients were females.

The mean systolic BP was 160±10.2 mm Hg in hypertensive group and 126±6.8 mm Hg in normotensive group. The mean diastolic BP was 108±6.2 mm Hg in hypertensive and 82±4.6 mm Hg in normotensive group. The mean systolic BP in the controls was 116±2.9 mm Hg and mean diastolic BP was 75.5±3.8 mm Hg.

In this study, CKD patients had significant anaemia with mean haemoglobin of about 7.39±2.40 gm/dl in CKD hypertensive group, 7.72±1.56 gm/dl in CKD normotensive group and 12.85±2.0 gm% in controls.

The average S. creatinine values in CKD hypertensives, CKD normotensives and controls are 7.44±5.35, 3.77±1.78 and 0.83±0.16 mg/dl.

The average eGFR values in CKD hypertensives, CKD normotensives and control groups are 14.59 ± 13, 22.21 ± 13.31 and 95.27 ± 17.04 ml/min/1.73 m^2.

In my study 80% of CKD hypertensives had LVH as compared to 64% normotensives. 26% of CKD with hypertensives and 8% of CKD normotensives had systolic dysfunction.

74% of CKD patients have diastolic dysfunction as compared to 16% in controls. This association was found to be extremely significant.

64% of CKD with normotension have diastolic dysfunction as compared to 16% in controls.

According to Pearson's correlation coefficient; the correlation between eGFR and Diastolic dysfunction was calculated and R value obtained was R= - 0.90682. This showed that there is a moderate negative correlation between eGFR and diastolic dysfunction.

CONCLUSION

- Left ventricular diastolic dysfunction is more significantly associated with the decline in eGFR than systolic dysfunction in CKD patients. This is found to occur at an earlier stage of CKD , even without LVH. Thus diastolic dysfunction is a much better predictor for cardiovascular mortality.

- The lower the eGFR, the more severe the LV diastolic dysfunction.

- LV diastolic dysfunction is more, if there is associated hypertension and anaemia. So, early identification and treatment of above conditions can retard the cardiovascular morbidity and mortality.

- Even in the absence of hypertension, LV diastolic dysfunction can occur in CKD. This emphasises on the need for correction of non-hemodynamic factors like secondary hyperparathyroidism, inflammation, oxidative stress, myocardial fibrosis, and altered mineral metabolism. Research should be focused on modalities that can intervene with the above factors in addition to the control of traditional hemodynamic factors.

- Echocardiography provides a simple, non-invasive investigation that can identify even asymptomatic patients at an earlier stage of CKD. So, earlier screening of CKD patients for LV diastolic dysfunction can be recommended.

BIBLIOGRAPHY

1. Michael Chonchol and David. M. Spiegel. The patient with Chronic Kidney Disease : Manual of Nephrology: – 7th edition pg 185 – 192

2. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA 2007;298:2038-2047

3. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

4. Hall YN, Hsu CY, Iribarren C, et al: The conundrum of increased burden of end-stage renal disease in Asians. *Kidney Int* 2005; 68:2310-2316.

5. Modi GK, Jha V. The incidence of end-stage renal disease in India: a population-based study. Kidney Int. 2006;70(12):2131-3

6. CKD registry of India: Indian Society of Nephrology. [online] Available from http://www.ckdri.org [Accessed September, 2012].

7. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

8. Fassbinder W, Brunner FP, Brynger H, Ehrich JH, Geelings W, Raine AF, et al. Combined report on regular dialysis and transplant in Europe XX1989. Nephrol Dial Transpl1991;6:5-35.

9. Bullock RE, Hassem AA, Simpson I et al. Cardiac abnormalities and exercise tolerance in patients receiving renal replacement therapy. BMJ 1984;28:1479-84.

10. Hughson M, Farris III AB, Douglas-Denton R, et al: Glomerular number and size in autopsy kidneys: The relationship to birth weight. *Kidney Int* 2003; 63:2113.

11. Kreidberg JA: Podocyte differentiation and glomerulogenesis. *J Am Soc Nephrol* 2003; 14:806-814.

12. Greger R: Physiology of renal sodium transport. *Am J Med Sci* 2000; 319:51-62.

13. Kidney Disease Outcome Quality Initiative: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 2002; 39(2 Suppl 2):S1-S246.

14. Longi, Fauci et al:Harrison's principles of Internal Medicine:18th edition; Chronic Kidney Disease, Chapter 280; Pg 2308-2321

15. Parfrey PS (editor): Cardiac disease in chronic uremia: Uremia related risk factors. *Semin Dial* 12: 1–132, 1999

16. Domanski M, Mitchell G, Pfeffer M, et al: Pulse pressure and cardiovascular disease-related mortality: Follow-up study of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 2002; 287:2677-2683.

17. Brenner and Rector's : The Kidney – 8th edition; Risk Factors and Kidney Disease, Chapter 18, Pg 633 – 649

18. Ronco C, McCullough P, Anker SD et al. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. Eur Heart J 2010; 31: 703–711.

19. Schrier RW. Cardiorenal versus renocardiac syndrome: is there a difference? Nat Clin Pract Nephrol 2007; 3: 637.

20. Das M, Aronow WS, McClung JA et al. Increased prevalence of coronary artery disease, silent myocardial ischemia, complex ventricular arrhythmias, atrial fibrillation, left ventricular hypertrophy, mitral annular calcium, and aortic valve calcium in patients with chronic renal insufficiency. Cardiol Rev 2006; 14: 14–17.

21. Sarnak MJ. Cardiovascular complications in chronic kidney disease. Am J Kidney Dis. 2003;41(Suppl 5):S11-S17.

22. Middleton RJ, Parfrey PS, Foley RN. Left ventricular hypertrophy in the renal patient. J Am Soc Nephrol. 2001;12:1079-1084.

23. Shulman NB, Ford CE, Hall WD, et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function: results from the Hypertension Detection and Follow-up Program. The Hypertension Detection and Follow up Program Cooperative Group. Hypertension. 1989;13(Suppl):I80-93.

24. Manjunath G, Tighiouart H, Ibrahim H, et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. J Am Coll Cardiol. 2003;41:47-55.

25. Manjunath G, Tighiouart H, Coresh J, et al. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. Kidney Int. 2003;63:1121-1129.

26. Henry RM, Kostense PJ, Bos G, et al. Mild renal insufficiency is associated with increased cardiovascular mortality: The Hoorn Study. Kidney Int. 2002;62:1402-1407.

27. Fellstrom BC, Jardine AJ, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis.N Engl J Med. 2009;360:1395-1407.

28. Nardi E, Palermo A, Mulè G, Cusimano P, Cottone S, Cerasola G. Left ventricular hypertrophy and geometry in hypertensive patients with chronic kidney disease. J Hypertens.2009;27:633-641.

29. Nardi E, Cottone S, Mulè G, Palermo A, Cusimano P, Cerasola G. Influence of chronic renal insufficiency on left ventricular diastolic function in hypertensives without left ventricular hypertrophy. J Nephrol. 2007;20:320-328.

30. Tucker B, Fabbian F, Giles M, Thuraisingham C, Raine AE, Baker LR. Left ventricular hypertrophy and ambulatory blood pressure monitoring in chronic renal failure. Nephrol Dial Transplant. 1997;12:724-728.

31. London GM, Marchais SJ et al, Cardiac hypertrophy and arterial alteration in ESRD: hemodynamic factors. Kidney Int 1993; 41(Suppl): S 42- S 49

32. Foley RN, Parfrey PS, Harnett JD, et al. Clinical and echocardiographic disease in patients starting end stage renal disease therapy. Kidney Int. 1995;47:186-192.

33. Levin A, Thompson C, Ethier J, et al. Left ventricular mass index increase in early renal disease: impact in decline in haemoglobin. Am J Kidney Dis. 1999;34:125-134.

34. Paoletti E, Bellino D, Casottana P, Rolla D, Cannella G. Left ventricular hypertrophy in nondiabetic predialysis CKD. Am J Kidney Dis. 2005;46:320-327.

35. Peterson GE, de Backer T, Gabriel A, et al. Prevalence and correlates of left ventricular hypertrophy in the African American Study of Kidney Disease Cohort Study. Hypertension.2007;50:1033-1039.

36. Cottone S, Mulè G, Guarneri M, et al. Endothelin-1 and F2-isoprostane relate to and predict renal dysfunction in hypertensivpatients. Nephrol Dial Transplant. 2009;24:497-503.

37. Ayerden Ebinç F, Ebina H, Derici U, et al. The relationship between adiponectin levels and proinflammatory cytokines and left ventricular mass in dialysis patients. J Nephrol.2009;22:216-223.

38. Kennedy DJ, Vetteth S, Periyasamy SM, et al. Central role for the cardiotonic steroid marinobufagenin in the pathogenesis of experimental uremic cardiomyopathy. Hypertension 2006;47:488-495.

39. Gutierrez O, Isakova T, Rhee E, et al. Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. J Am Soc Nephrol.2005;16:2205-2215.

40. Gutiérrez OM, Januzzi JL, Isakova T, et al. Fibroblast growth factor-23 and left ventricular hypertrophy in chronic kidney disease. Circulation. 2009;119:2545-2552.

41. Mirza M, Larsson A, Melhus H, Lind L, Larsson T. Serum intact FGF-23 associate with left ventricular mass, hypertrophy and geometry in an elderly population. Atherosclerosis 2009;207:546-551.

42. Mall G, Huther W, Schneider J, Lundin P, Ritz E. Diffuse intermyocardiocytic fibrosis in uraemic patients. Nephrol Dial Transplant. 1990;5:39-44.

43. London GM. Left ventricular alteration and end-stage renal disease. Nephrol Dial Transplant. 2002;17:29-36.

44. Fathi R, Isbel N, Haluska B, Case C, Johnson DW, Marwick TH. Correlates of subclinical left ventricular dysfunction in ESRD. Am J Kidney Dis. 2003;41:1016-1025.

45. Ahmed A, Rich M, Sanders P, et al. Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity matched study. Am J Cardiol.2007;99:393-398.

46. Tsioufis C, Vezali E, Tsiachris D, et al. Left ventricular hypertrophy versus chronic kidney disease as predictors of cardiovascular events in hypertension: a Greek 6-year-follow-up study. J Hypertens. 2009;27:744-752.

47. Patrik S. Parfrey and Robert N. Foley, The Clinical Epidemiology of Cardiac Disease in Chronic Renal Failure J Am Soc Nephrol 10: 1606–1615, 1999,

48. Meyeon Park, Chi-yuan Hsu, Yongmei Li, Associations between Kidney Function and Subclinical Cardiac Abnormalities in CKD, J Am Soc Nephrol. Sep 28, 2012; 23(10): 1725–1734.

49. Roberto Pecoits-Filho, Silvio H. Barberato, Echocardiography in Chronic Kidney: Diagnosis and Prognostic Implications, Nephron Clinical Practice 2010;114: c242 – c247

50. Giovanni Cerasola , Emilio Nardi , Alessandro Palermo et al, Epidemiology and pathophysiology of left ventricular abnormalities in chronic kidney disease: a review JNEPHROL 2011; 24(01): 1- 10.

51. Rathod Nitin R, Ghodasara Malay K , Shah Harsh D Assessment of cardiac dysfunction by 2D echocardiography in patients of chronic kidney disease. JPBMS, 2012, 17 (07)

52. E. B. Arodiwe, I. I. Ulasi, C. K. Ijoma ,et al Left Ventricular Diastolic Function in a Predialysis Patient Population. West African Journal of Medicine 2010; 29(4): 225–22.

53. Takenori Otsuka (MD), Makoto Suzuki (MD, FJCC), Hisao Yoshikawa (MD),et al Left ventricular diastolic dysfunction in the early stage of chronic kidney disease. Journal of Cardiology (2009) 54, 199—204.

54. S Agarwal, P Dangri, OP Kalra et al Echocardiographic Assessment of Cardiac Dysfunction in Patients of Chronic Renal Failure. JIACM 2003; 4(4): 296-303.

PROFORMA

PARTICULARS OF THE PATIENT :

Name: Case No:

Age/ Sex:

Address:

Contact No:

PRESENTING COMPLAINTS:

Breathlessness Chest pain

Oliguria Altered sensorium

Abdominal pain/ vomiting Others

Volume overload Easy fatigue ability

PAST HISTORY:

Duration of CKD:

Treatment details:

MEDICAL HISTORY:

Hypertension

Diabetes

Smoker/ Alcoholic

CLINICAL EXAMINATION:

Pallor : Pedal oedema:

Height : Weight: BMI:

Vitals: BP MAP (Mean Arterial Pressure):

System Examination:

CVS:

RS:

Abdomen:

CNS:

INVESTIGATIONS:

Hb%

Urine: Albumin Sugar Deposits

24 hour urinary protein:

RBS

Lipid profile: S. cholesterol: LDL: HDL: TG:

Blood Urea:

Serum creatinine:

MDRD (Modification of Diet Renal Disease study) equation :

eGFR (ml / min / 1.73 m^2) = 186.3 × (Plasma creatinine) $^{-1.154}$× (age) $^{-0.203}$

x 0.742 if female

ECG:

USG Abdomen: Right kidney size: Left kidney size:

ECHOCARDIOGRAPHY:

LVEF:

E/A ratio:

LVH: concentric eccentric:

MASTER CHART

S.NO	NAME	AGE	SEX	WEIGHT	HEIGHT	BMI	CREATININ	eGFR	BP	Hb	DD	LVEF	LVH
1	Akbar	69	M	54	1.5	24	2.5	27.39704	134/88	7.6	_	56	N
2	Alaguraja	58	M	59	1.47	27.30344	15.9	3.356021	200/140	3.9	2.3	54	C
3	Angulakshmi	68	F	55	1.52	23.8054	2.6	19.4867	154/92	9.6	_	58	C
4	Aravind Raja	42	M	69	1.62	26.29172	0.8	112.8567	160/110	13	-	56	C
5	Arokyasamy	66	M	60	1.58	24.03461	15	3.496521	150/90	4.2	2.2	40	C
6	Arumugam	45	F	50	1.49	22.52151	2.2	25.6956	160/90	8	1.2	49	C
7	Arumugam	52	M	60	1.54	25.29938	1.5	52.31845	150/96	12.8	_	53	C
8	Azhagar	57	M	56	1.63	21.0772	1.8	41.60886	132/82	9.1	0.7	54	N
9	Bagyalakshmi	65	F	54	1.54	22.76944	0.6	106.8092	130/80	11.8	-	63	N
10	Bagyam	69	F	42	1.56	17.25838	0.7	88.32573	100/70	11.5	-	54	N
11	Balamurugan	43	M	58	1.6	22.65625	0.9	98.04442	116/76	12.8	-	57	N
12	Balasubramani	47	M	56	1.57	22.71897	5.3	12.44408	100/60	8.6	_	46	C
13	Baskaran	65	M	63	1.59	24.9199	1	79.83465	108/84	12.4	0.9	55	N
14	Bharani	63	M	58	1.54	24.45606	1	80.34276	148/98	14	-	52	N
15	Bose	62	M	56	1.56	23.01118	6.7	8.975673	116/84	6.3	2.3	58	N
16	Chandramohan	67	M	64	1.56	26.29849	0.8	102.6488	114/82	12.7	-	54	N
17	Chandran	35	M	42	1.57	17.03923	4.5	15.95731	118/88	7.1	1.8	50	C
18	Chidambaran	51	M	68	1.58	27.23922	1	83.8641	146/96	14	-	46	N
19	Chinnathambi	63	M	58	1.59	22.94213	1.6	46.70811	132/86	9.2	_	61	N
20	Dhiraviam	42	M	48	1.59	18.98659	6.4	10.24145	142/92	8.3	1.9	56	C
21	Dinakaran	69	M	50	1.5	22.22222	0.9	89.06983	110/70	13.1	-	54	N
22	Eswari	65	F	48	1.49	21.62065	10	4.155233	150/90	5.9	2.2	52	C
23	Ganesh	44	M	42	1.59	16.61327	10.6	5.667467	160/110	5.4	2.2	39	C
24	Gnanasoundari	58	F	58	1.5	25.77778	4.7	10.16342	114/88	6.8	1.4	51	C
25	Gomathiammal	48	F	46	1.54	19.39619	0.6	113.5895	100/80	11	-	59	N
26	Gomathy	53	F	50	1.54	21.08281	3.2	16.13042	120/80	8.6	1.6	58	N
27	Gopal	43	M	56	1.58	22.4323	3.6	19.79911	140/100	9	1.3	45	C
28	Gowri	68	F	52	1.5	23.11111	7.9	5.404503	124/76	5	2.3	55	C
29	Gunaseelan	63	M	61	1.58	24.43519	0.9	90.72999	130/76	12.9	-	56	N
30	Gunasekhar	54	M	51	1.6	19.92188	3.7	18.31606	170/100	9.5	1.4	55	C
31	Guru	67	M	52	1.6	20.3125	2.4	28.89056	100/70	8	_	52	C
32	Habidhulla	57	M	56	1.6	21.875	0.9	92.5922	110/80	13	-	56	N
33	James	37	M	45	1.58	18.02596	1.7	48.52101	120/80	7.9	_	52	C
34	John Manoj	35	M	67	1.59	26.50212	0.9	102.2283	160/96	12.5	-	59	N
35	Kailarajan	44	M	66	1.55	27.47138	1	86.41556	160/100	13.5	-	53	C
36	Kaliammal	50	F	40	1.5	17.77778	2.3	23.89417	150/90	10.8	_	58	N
37	Kalimuthu	60	M	59	1.59	23.33768	18.2	2.851844	160/80	3.6	2.4	52	C
38	Kannan	59	M	52	1.59	20.56881	2.6	27.03029	150/90	8.3	1.1	52	N
39	Karikalan	65	M	69	1.6	26.95313	0.9	90.1562	112/78	12.6	0.8	54	N
40	Kartheeshan	59	M	58	1.59	22.94213	1.7	44.13589	110/80	8.9	0.8	54	C
41	Karthikeyan	51	M	52	1.55	21.64412	3.6	19.12507	136/74	8.4	1.3	42	C
42	Karuppiah	48	M	45	1.49	20.26936	1.9	40.47988	116/84	7	0.6	60	N
43	Karuppusamy	38	M	45	1.6	17.57813	16.7	3.455429	200/120	6.1	2.3	41	C
44	Kesavan	43	M	62	1.58	24.83576	0.9	98.04442	160/100	14	-	53	N
45	Koothammal	55	F	53	1.5	23.55556	11.7	3.586218	170/110	4.6	2.3	46	C
46	Krishnamoorthy	49	M	53	1.63	19.94806	0.8	109.3798	94/66	14	-	58	N
47	Krishnan	67	M	54	1.58	21.63115	2	35.65587	126/76	8.9	_	54	C
48	Kumar	64	M	72	1.59	28.47989	1	80.08632	160/100	12.4	0.7	57	C
49	Lakshmanan	69	M	55	1.53	23.49524	0.9	89.06983	160/100	14	-	52	C
50	Latha	36	F	46	1.45	21.87872	7	7.070404	110/70	5.4	2.4	59	N

51	Madasamy	56	M	50	1.57	20.2848	2.3	31.47	190/120	10	0.9	47	C
52	Mahalakshmi	52	F	49	1.58	19.62826	0.7	93.54594	146/96	12.8	-	64	N
53	Malasamy	63	M	58	1.61	22.37568	6.4	9.432244	150/108	6.3	1.9	54	C
54	Maniappan	45	M	54	1.58	21.63115	2	38.65646	120/80	9.4	_	58	N
55	Manikalai	46	M	53	1.58	21.23057	4.3	15.90928	150/90	9	1.4	45	C
56	Maniratinam	52	M	60	1.58	24.03461	1	83.53417	146/94	12.8	-	52	N
57	Mariappan	42	M	51	1.59	20.17325	0.8	112.8567	120/90	12.8	-	65	N
58	Marimuthu	66	M	63	1.59	24.9199	0.8	102.9626	158/92	13.2	0.9	53	N
59	Mariyappan	61	M	50	1.59	19.7777	23	2.169487	170/110	3.2	2.5	62	C
60	Meenakshi	35	F	50	1.47	23.13851	3.2	17.54801	180/100	6.5	1.3	50	C
61	Mohammed Jinnah	45	M	56	1.58	22.4323	2.6	28.55824	140/92	9.6	1	65	N
62	Mohammed Naseer	36	M	49	1.47	22.67574	2.7	28.60814	110/76	8.2	1.1	57	N
63	Mookammal	62	F	48	1.56	19.72387	0.7	90.26473	150/94	12.2	-	51	N
64	Mookan	36	M	49	1.63	18.44255	6.4	10.567	90/60	7.6	_	40	C
65	Moorthy	46	M	52	1.56	21.36752	1.9	40.83113	110/76	8	_	59	N
66	Muniyandi	54	M	53	1.59	20.96436	1.9	39.52349	100/70	7.5	0.7	58	N
67	Muniyandi	68	M	65	1.6	25.39063	0.9	89.33419	140/96	14.5	0.8	52	N
68	Muniyappan	64	M	57	1.62	21.71925	2.5	27.81862	190/120	7.2	1.1	52	C
69	Murugesan	39	M	65	1.58	26.03749	0.9	100.0071	110/80	13.8	-	58	N
70	musthafa hameed	70	M	56	1.55	23.30905	10.7	5.102101	140/90	6.5	2.1	52	N
71	Muthu	47	M	57	1.53	24.34961	1.9	40.65326	116/88	9.3	_	55	N
72	Mydeen	50	M	55	1.53	23.49524	10.1	5.838954	180/110	6.8	2.1	40	C
73	Nadiammal	58	F	56	1.54	23.61275	15.6	2.545512	160/100	5	2.3	40	C
74	Nagaraj	52	M	58	1.59	22.94213	0.9	94.33402	90/60	12.6	-	59	N
75	Nagendran	59	M	53	1.54	22.34778	4.1	15.98002	136/80	7.7	_	57	N
76	Narasimhan	53	M	54	1.58	21.63115	0.8	107.6512	98/70	12.7	-	58	N
77	Naseema	56	F	41	1.57	16.63353	0.7	92.14918	126/78	11.3	-	65	N
78	Natarajan	41	M	54	1.62	20.57613	8.4	7.519681	156/96	7.9	2	56	C
79	Noor Jahan	59	F	55	1.6	21.48438	0.8	78.15701	150/90	11.6	-	51	N
80	Palaniappan	54	M	43	1.49	19.3685	2.9	24.26217	110/78	8.3	1.2	53	C
81	Palanivel	59	M	45	1.53	19.22338	5.1	12.42207	100/68	7.4	2	52	C
82	Pandiyan	68	M	72	1.54	30.35925	6.8	8.659609	150/100	8.2	2	52	C
83	Parthi Sarathi	68	M	49	1.59	19.38214	6.5	9.122451	110/74	6.6	2.2	59	N
84	Periyasamy	68	M	57	1.59	22.54658	1.7	42.88205	120/80	8	_	64	N
85	Peryakarupusamy	65	M	42	1.49	18.91807	7.6	7.686569	150/100	6	2.2	53	N
86	Petchiammal	38	F	45	1.56	18.49112	0.6	119.1061	140/100	11.8	-	56	C
87	Prabhu	57	M	49	1.56	20.13478	5.6	11.22952	110/72	7.6	_	54	N
88	Prema	63	F	45	1.59	17.79993	3.6	13.59495	116/78	7.8	2	57	N
89	Premkumar	58	M	62	1.6	24.21875	0.9	92.26588	156/94	13.8	-	58	N
90	Pushpavalli	70	F	50	1.48	22.82688	7	6.177585	160/90	7.8	2	41	C
91	Raghavan	52	M	64	1.57	25.96454	0.9	94.33402	150/100	15	-	51	C
92	Raj Kumar	52	M	47	1.54	19.81784	3.3	21.06197	120/80	6.4	1.3	58	N
93	Rajappan	69	M	45	1.53	19.22338	15.6	3.311774	160/90	3.9	2.4	58	N
94	Rajasekhar	52	M	58	1.56	23.833	0.8	108.0683	150/100	14.6	-	54	C
95	Rajaselvam	63	M	48	1.53	20.50493	0.7	89.97202	148/100	12	0.7	53	C
96	Rajendran	35	M	47	1.56	19.31295	14.5	4.135694	180/100	8.5	2.2	48	C
97	Rajvel	68	M	54	1.61	20.83253	2	35.5488	130/80	8.3	0.9	53	N
98	Ramachandran	43	M	56	1.48	25.56611	2.2	34.95127	110/70	9.6	_	51	C
99	Ramar	43	M	50	1.64	18.59012	4.3	16.12858	96/72	7.9	_	54	C
100	Ramasamy	45	M	54	1.62	20.57613	5.7	11.54333	140/94	7.3	1.7	53	N

101	Ramasamy	47	M	54	1.56	22.18935	1	85.26622	124/80	13.5	-	56	N
102	Ramkrishna	60	M	51	1.58	20.42942	5.8	10.67216	132/78	7.1	2.1	54	N
103	Raniammal	48	F	65	1.53	27.7671	4.2	12.02528	90/60	9.5	2.1	55	N
104	Rathinam	34	M	53	1.57	21.50189	1.5	57.03131	160/100	9	0.7	58	C
105	Rathinam	36	M	54	1.59	21.35991	1	90.00848	170/100	14	-	57	C
106	Ravichandran	55	M	45	1.58	18.02596	7.8	7.716886	160/100	4.5	2.1	42	C
107	Remadevi	66	F	65	1.55	27.05515	0.8	76.39827	160/96	12.5	0.8	54	N
108	Ronald	51	M	65	1.63	24.4646	0.9	94.7066	148/96	13.4	-	51	N
109	Santhanalakshmi	69	F	55	1.52	23.8054	4.3	10.87196	156/98	10.1	_	56	C
110	Santhanamal	67	F	50	1.53	21.35931	4.1	11.55503	170/110	9.5	_	42	C
111	Saral salima	38	F	48	1.56	19.72387	3.6	15.06425	180/100	8	1.4	54	C
112	Saraswathi	46	F	53	1.53	22.64086	5	9.918946	150/96	8.8	1.8	59	C
113	Saratha	54	F	56	1.47	25.91513	11.5	3.67194	180/110	6.2	2.3	54	C
114	Sathyammal	54	F	46	1.58	18.42653	0.7	92.832	120/80	12.4	-	64	N
115	Savithri	45	F	59	1.5	26.22222	1.3	47.15459	160/96	9.4	0.8	56	C
116	Selvaratinam	58	M	56	1.56	23.01118	0.9	92.26588	100/60	13.5	-	62	N
117	Sethu	63	M	56	1.59	22.15102	11.7	4.701758	160/110	5.5	2.1	47	C
118	Sethumathy	48	F	56	1.47	25.91513	0.6	113.5895	160/100	12.6	-	60	C
119	Sethupathy	66	F	48	1.5	21.33333	5.1	9.009763	170/100	8.1	2	55	C
120	Sethuraman	65	M	54	1.59	21.35991	2.5	27.7312	170/100	9.7	1.2	24	C
121	Shahul Hameed	63	M	51	1.55	21.22789	4.6	13.80779	128/86	7.7	_	55	N
122	Shamsath Beegum	66	F	42	1.6	16.40625	5.9	7.615284	100/60	8.9	_	60	N
123	Shankar	66	M	57	1.48	26.02264	4	16.07194	110/70	9.2	_	57	N
124	Shanmugasundaram	37	M	55	1.56	22.60026	0.8	115.7983	100/70	12.6	-	60	N
125	Sindhuja	64	F	53	1.48	24.19649	4	12.0001	110/70	6.4	2	45	C
126	Sivan	63	M	75	1.6	29.29688	1	80.34276	150/98	12.8	-	53	N
127	Sounderapandy	58	M	57	1.58	22.83288	0.9	92.26588	100/70	12.4	-	54	N
128	Srinivasan	63	M	60	1.6	23.4375	3.1	21.77285	126/78	7.8	_	43	C
129	Stalin Raja	50	M	54	1.57	21.90758	2.8	25.66265	138/82	8.5	1.3	48	C
130	Subadra	68	F	46	1.59	18.19548	5	9.162333	90/70	8	2.2	64	N
131	Subbiah	62	M	58	1.56	23.833	4.7	13.51314	134/78	8.6	0.8	57	N
132	Subramani	41	M	60	1.64	22.30815	5.8	11.5298	120/86	7.4	1.8	53	C
133	Sujatha	49	F	56	1.52	24.23823	1.5	39.29141	100/70	8.2	0.8	56	N
134	Sumithra	62	F	48	1.58	19.22769	0.7	90.26473	100/60	10.6	0.9	54	N
135	Sundaram	56	M	63	1.6	24.60938	12.4	4.503209	180/100	4.8	2.1	44	C
136	Tamilnila	46	F	38	1.49	17.11635	0.7	95.90335	110/70	11.6	-	56	N
137	Tamilselvi	61	F	54	1.4	27.55102	4.3	11.14736	126/86	6	2.1	54	C
138	Thirunesan	42	M	41	1.6	16.01563	4.2	16.65189	158/98	8.6	1.4	51	C
139	Umma	38	F	42	1.46	19.70351	2.1	28.05948	130/80	6.2	1.1	46	C
140	Vallarmathi	59	F	43	1.49	19.3685	6.2	7.357221	110/70	6.4	2.3	54	N
141	Veerajeeyan	63	M	65	1.57	26.37024	2.2	32.34379	148/98	10.1	0.9	63	N
142	Veerammal	54	F	54	1.49	24.32323	3.2	16.06933	106/86	5.1	1.4	52	N
143	Veerammal	45	F	46	1.57	18.66201	0.7	96.3322	150/94	12.4	-	63	N
144	Velu	52	M	59	1.56	24.24392	3.3	21.06197	160/96	9.4	1.3	60	N
145	Venkateshwar	36	M	40	1.58	16.02307	4.6	15.46895	190/110	6.3	1.3	42	C
146	Vigneshwaran	60	M	52	1.62	19.81405	0.8	104.9741	120/80	13.2	-	56	N
147	Vijayalakshmi	45	F	49	1.54	20.66116	4.9	10.19831	120/80	6.9	2.1	45	C
148	Vijayan	55	M	58	1.59	22.94213	5.2	12.32115	140/90	7.9	1.5	51	C
149	Vishnupriya	37	F	40	1.5	17.77778	0.7	100.2371	120/80	12.6	-	54	N
150	Williams	60	M	62	1.57	25.15315	12.7	4.31975	190/100	4	2.2	58	C

KEY TO MASTER CHART

M- Males

F-Females

BMI- body mass index

eGFR- estimated glomerular filtration rate

DD- diastolic dysfunction

LVEF- left ventricular ejection fraction

Hb- Hemoglobin

BP- Blood pressure

LVH- Left ventricular hypertrophy

N- Normal

C- Concentric LVH